2007

Access DB# 93741

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: K. Weddington Examiner #: 68082 Date: 8-19-02
Art Unit: 1614 Phone Number 308-4650 Serial Number: 09/782,924
Mail Box and Bldg/Room Location: _____ Results Format Preferred (circle): PAPER DISK E-MAIL

If mor than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

_____

Earliest Priority Filing Date: _____

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

A method for treating sepsis pancreatitis burns or trauma with a cyclooxygenase-2 inhibitor.

The cyclooxygenase inhibitor is selected from

NS-398
Celecoxib
MK-0966
parecoxib

Mary Jane Ruhl
Tech. Info. Specialist, STIC
TC-1600
CM-1, Room 6A-06
Phone: 605-1155

****

STAFF USE ONLY

Searcher: Ruhl / Beverly C4994
Searcher Phone #: _____
Searcher Location: _____
Date Searcher Picked Up: _____
Date Completed: 9/4/02
Searcher Prep & Review Time: _____
Clerical Prep Time: _____
Online Time: _____

Type of Search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) _____
Bibliographic _____
Litigation _____
Fulltext _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN _____
Dialog _____
Questel/Orbit _____
Dr.Link _____
Lexis/Nexis _____
Sequence Systems _____
WWW/Internet _____
Other (specify) _____

PTO-1590 (8-01)

FILE 'REGISTRY' ENTERED AT 16:21:54 ON 03 SEP 2002
L1 4 SEA ABB=ON (NS 398 OR CELECOXIB OR MK 0966 OR PARECOXIB)/CN

FILE 'HCAPLUS' ENTERED AT 16:22:30 ON 03 SEP 2002
L2 17800 SEA ABB=ON PLU=ON (TREAT? OR THERAP?)(5A)(SEPS!S OR PANCREAT? OR PANCREAS(3A)(DISEAS? OR DISORDER) OR BURN OR TRAUMA OR WOUND OR INJUR?)
L3 23 SEA ABB=ON PLU=ON L2 AND (L1 OR NS398 OR NS 398 OR CEL!COXIB OR MK 0966 OR MK0966 OR PAR!COXIB)

=> d l3 ibib abs hitrn 1-23

L3 ANSWER 1 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:641475 HCAPLUS
TITLE: Renal failure associated with the use of **celecoxib** and rofecoxib
AUTHOR(S): Ahmad, Syed R.; Kortepeter, Cindy; Brinker, Allen; Chen, Min; Beitz, Julie
CORPORATE SOURCE: Division of Drug Risk Evaluation, Office of Drug Safety, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD, USA
SOURCE: Drug Safety (2002), 25(7), 537-544
CODEN: DRSAEA; ISSN: 0114-5916
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: **Celecoxib** and rofecoxib are two relatively new nonsteroidal anti-inflammatory drugs (NSAIDs) that selectively inhibit the cyclo-oxygenase-2 (COX-2) isoenzyme at therapeutic concns. The nephrotoxic potential of selective COX-2 inhibitors has not been clearly established. This study was conducted in order to understand the assocn. between acute renal failure and the two COX-2 inhibitors **celecoxib** and rofecoxib. Methods: A search was performed in the US Food and Drug Administration's (FDA) Adverse Event Reporting System (AERS) to identify cases of renal failure submitted to the FDA. A MEDLINE search of the English language literature was also performed to identify published cases of renal failure assocd. with **celecoxib** and rofecoxib. Results: One hundred twenty-two and 142 domestic US cases of **celecoxib** and rofecoxib-assocd. renal failure, resp., were identified in the AERS database. The literature search identified 19 cases of acute renal impairment in assocn. with **celecoxib** and rofecoxib. In addn., drug regulatory authorities in the UK, Canada, and Australia have received about 50 reports of renal failure with **celecoxib** and rofecoxib. Descriptive statistics of the AERS cases have been summarised in this report. Conclusions: Data from AERS and published case reports suggest that use of both these drugs is assocd. with renal effects similar to that of conventional nonselective NSAIDs. Physicians should be aware that serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short-term therapy with **celecoxib** and rofecoxib. Patients at greatest risk for renal injury are those with pre-existing renal impairment, heart failure, liver dysfunction, those taking diuretics and/or ACE inhibitors, and the elderly. Kidney function should be monitored closely for any signs of potential renal **injuries** soon after initiating **treatment** with these agents, esp. in high-risk populations. In addn., healthcare practitioners should adequately warn patients of the signs and symptoms of serious renal toxicity, and of the need for them to see their physician promptly if they occur. **Celecoxib** and rofecoxib are not recommended for use in patients with advanced renal disease.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:594822 HCAPLUS
TITLE: Preparation of nicotinamide biaryl derivatives as inhibitors of PDE4 isozymes
INVENTOR(S): Chambers, Robert James; Magee, Thomas Victor; Marfat, Anthony
PATENT ASSIGNEE(S): Pfizer Productors Inc., USA
SOURCE: PCT Int. Appl., 224 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002060875	A1	20020808	WO 2001-IB2341	20011206

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-265492P P 20010131
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; g = 0-1; j = 0-1; provided that when j = 0, n must be 2; k = 0-1; m = 0-2; n = 1-2; W1 = 0, SOt (t = 0-2), NR3; W2 = OCR9R10, or absent; Y = CR1, NOk (k = 0-1); R9, R10 = H, F, CF3, etc.; or R9 and R10 are taken together, but only in the case where m = 1, to form a spiro moiety; R7, R8 have the same meaning as R9, R10 except that one of them must be H; R1, R2 = H, F, Cl, etc.; R3 = H, alkyl, Ph, etc.; R4-R6 = H, F, Cl, etc.; Q1 = Ph, benzodioxyl, etc.; Q2 = biaryl moiety], useful as inhibitors of PDE4 in the treatment of diseases regulated by the activation and degranulation of eosinophils, esp. asthma, chronic bronchitis, and chronic obstructive pulmonary disease, were prepd. E.g., a multi-step synthesis of the amide II, starting from Me 3-bromobenzoate and 4-formylbenzeneboronic acid, was given. Compds. I showed anti-inflammatory activity at 0.0001 .mu.M to 20.0 .mu.M in whole blood assay for LTE4.

IT **162011-90-7**, Rofecoxib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination with; prepn. of biaryl nicotinamides as inhibitors of PDE4 isoenzymes)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

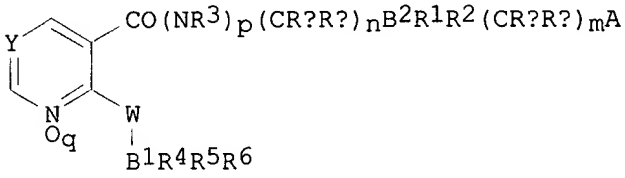
L3 ANSWER 3 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:591707 HCAPLUS

DOCUMENT NUMBER: 137:140509
TITLE: Preparation of nicotinamides and mimetics as inhibitors of phosphodiesterase IV isozymes
INVENTOR(S): Chambers, Robert J.; Magee, Thomas V.; Marfat, Anthony
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 180 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1229034	A1	20020807	EP 2002-2250202	20020111
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002111495	A1	20020815	US 2002-62811	20020131

PRIORITY APPLN. INFO.: US 2001-265240P P 20010131
US 1997-43403P P 19970404
US 1998-105120P P 19981021

GI



I

AB Title compds. [I; p, q = 0, 1; m = 0-2; n = 1, 2; A = CO2R7, CONR9CO2R7, CONR7R9, OP(O)(OH)2, SO3H, acylsulfonamido, etc.; W = O, S, SO, SO2, NR3; Y = N, NO, CR11; R1, R2 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, etc.; R3 = H, alkyl, Ph, PhCH2, etc.; R4-R6 = H, F, Cl, alkynyl, cyano, NO2, etc.; R7 = H, (substituted) alkyl, alkenyl, alkynyl; R9 = H, alkyl, cycloalkyl, Ph, PhCH2, pyridyl, etc.; R11 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, fluoroalkoxy, etc.; Ra, Rb = H, F, CF3, alkyl, (substituted) cycloalkyl, Ph, PhCH2; B1, B2 = 3-7 membered (hetero)cyclyl, 7-12 membered poly(hetero)cyclyl; pairs of variables may form rings; with provisos], were prepd. (no data). Thus, Me 2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionate was suspended in Me3COH. Aq. NaOH was added to the suspension, and the reaction mixt. was refluxed 1 h to give 2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionic acid.

IT **162011-90-7**, Rofecoxib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy; prepn. of nicotinamides and mimetics as inhibitors of phosphodiesterase IV isoenzymes)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

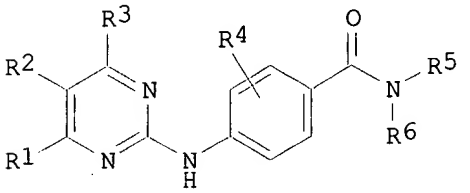
L3 ANSWER 4 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:449662 HCAPLUS
DOCUMENT NUMBER: 137:33310
TITLE: Preparation of anilinopyrimidines as IKK inhibitors
INVENTOR(S): Kois, Adam; MacFarlane, Karen J.; Satoh, Yoshitaka;

Bhagwat, Shripad S.; Parnes, Jason S.; Palanki, Moorthy S. S.; Erdman, Paul E.
PATENT ASSIGNEE(S): Signal Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 194 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002046171	A2	20020613	WO 2001-US46403	20011205

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-251816P P 20001206
OTHER SOURCE(S): MARPAT 137:33310
GI



I

AB The title compds. [I; R1 = (un)substituted (hetero)aryl; R2 = H; R3 = H, alkyl; R4 = halo, OH, alkyl, alkoxy; R5, R6 = R8, (CH2)aCOR9, (CH2)aCO2R9, etc.; or NR5R6 = (un)substituted heterocycle; R8, R9 = H, alkyl, aryl, etc.; a = 0-4] having activity as inhibitors of IKK, particularly IKK-2, were prepd. E.g., a multi-step synthesis of I [R1 = 4-ClC6H4; R2-R6 = H] having an IC50 of .ltoreq. 1 .mu.M in the IKK-2 enzyme assay, was given. Such compds. I have utility in the treatment of a wide range of conditions that are responsive to IKK inhibition. Thus, methods of treating such conditions are also disclosed, as are pharmaceutical compns. contg. one or more compds. of the above compds.

IT **162011-90-7**, Rofecoxib **169590-42-5, Celecoxib**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiinflammatory agent; prepn. of anilinopyrimidines as IKK inhibitors)

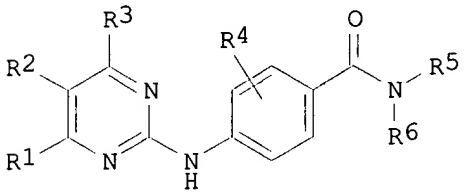
L3 ANSWER 5 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:449661 HCAPLUS
DOCUMENT NUMBER: 137:33309
TITLE: Preparation of anilinopyrimidines as JNK pathway inhibitors
INVENTOR(S): Kois, Adam; MacFarlane, Karen J.; Satoh, Yoshitaka; Bhagwat, Shripad S.; Parnes, Jason S.; Palanki, Moorthy S. S.; Erdman, Paul E.

PATENT ASSIGNEE(S): Signal Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 199 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002046170	A2	20020613	WO 2001-US46402	20011205

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-251904P P 20001206
OTHER SOURCE(S): MARPAT 137:33309
GI



I

AB The title compds. [I; R1 = (un)substituted (hetero)aryl; R2 = H; R3 = H, alkyl; R4 = halo, OH, alkyl, alkoxy; R5, R6 = R8, (CH2)aCOR9, (CH2)aCO2R9, etc.; or NR5R6 = (un)substituted heterocycle; R8, R9 = H, alkyl, aryl, etc.; a = 0-4] having activity as inhibitors of the JNK pathway, were prepd. E.g., a multi-step synthesis of I [R1 = 4-ClC6H4; R2-R6 = H] having an IC50 of .ltoreq. 10 .mu.M in the JNK2 assay, was given. Such compds. I have utility in the treatment of a wide range of conditions that are responsive to inhibition of the JNK pathway. Thus, methods of treating such conditions are also disclosed, as are pharmaceutical compns. contg. one or more compds. of the above compds.

IT **162011-90-7**, Rofecoxib **169590-42-5**, **Celecoxib**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiinflammatory agent; prepn. of anilinopyrimidines as JNK pathway inhibitors)

L3 ANSWER 6 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:393711 HCAPLUS
TITLE: Recovery of ischaemic injured porcine ileum: Evidence for a contributory role of COX-1 and COX-2
AUTHOR(S): Blikslager, A. T.; Zimmel, D. N.; Young, K. M.; Campbell, N. B.; Little, D.; Argenzio, R. A.
CORPORATE SOURCE: College of Veterinary Medicine, North Carolina State University, Raleigh, NC, 27606, USA

SOURCE: Gut (2002), 50(5), 615-623
CODEN: GUTTAK; ISSN: 0017-5749
PUBLISHER: BMJ Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have previously shown that the non-selective cyclooxygenase (COX) inhibitor indomethacin retards recovery of intestinal barrier function in ischemic injured porcine ileum. However, the relative role of COX-1 and COX-2 elaborated prostaglandins in this process is unclear. To assess the role of COX-1 and COX-2 elaborated prostaglandins in the recovery of intestinal barrier function by evaluating the effects of selective COX-1 and COX-2 inhibitors on mucosal recovery and eicosanoid prodn. Porcine ileal mucosa subjected to 45 min of ischemia was mounted in Ussing chambers, and transepithelial elec. resistance was used as an indicator of mucosal recovery. Prostaglandins E1 and E2 (PGE) and 6-keto-PGF1.alpha. (the stable metabolite of prostaglandin I2 (PGI2)) were measured using ELISA. Thromboxane B2 (TXB2, the stable metabolite of TXA2) was measured as a likely indicator of COX-1 activity. Ischemic injured tissues recovered to control levels of resistance within three hours whereas tissues treated with indomethacin (5.times.10-6 M) failed to fully recover, assocd. with inhibition of eicosanoid prodn. **Injured** tissues **treated** with the selective COX-1 inhibitor SC-560 (5.times.10-6 M) or the COX-2 inhibitor **NS-398** (5.times.10-6 M) recovered to control levels of resistance within three hours, assocd. with significant elevations of PGE and 6-keto-PGF1.alpha. compared with untreated tissues. However, SC-560 significantly inhibited TXB2 prodn. whereas **NS-398** had no effect on this eicosanoid, indicating differential actions of these inhibitors related to their COX selectivity. The results suggest that recovery of resistance is triggered by PGE and PGI2, which may be elaborated by either COX-1 or COX-2.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:380282 HCAPLUS
TITLE: Role for both spinal cord COX-1 and COX-2 in maintenance of mechanical hypersensitivity following peripheral nerve injury
AUTHOR(S): Ma, Weiya; Du, Wei; Eisenach, James C.
CORPORATE SOURCE: Department of Anesthesiology and Center for the Study of Pharmacologic Plasticity in the Presence of Pain, Pain Mechanisms Laboratory, Wake Forest University School of Medicine, Winston-Salem, NC, 27157-1009, USA
SOURCE: Brain Research (2002), 937(1,2), 94-99
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) in **treating** neuropathic pain caused by nerve **injury** has been controversial. In the present study, 4 wk following partial sciatic nerve ligation, a single intrathecal injection of the cyclooxygenase (COX)-1 preferring inhibitor ketorolac (50 .mu.g) significantly attenuated tactile allodynia for 6 days. The COX-2 preferring inhibitor, **NS-398** (60 .mu.g) significantly reversed tactile allodynia 2 h following injection but this anti-allodynic effect did not last greater than 24 h. Surprisingly, the non-selective COX inhibitor, piroxicam (60 .mu.g) was without effect. These data agree with previous studies suggesting that spinal prostaglandin synthesis is important in the

maintenance of hypersensitivity states following nerve injury. They differ from results in other models by suggesting that both COX isoenzymes are important in this spinal process, and for the first time demonstrate a remarkably long duration of action from a single intrathecal injection of ketorolac. Inhibition of spinal COX may be an important mechanism of action in treating some patients with neuropathic pain following peripheral nerve injury.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:339701 HCAPLUS
TITLE: NSAID inhibition of RGM1 gastric monolayer wound re-epithelialization: comparison of selective Cox-2 versus non-selective Cox inhibitors
AUTHOR(S): Giap, Andrew Q.; Tarnawski, Andrzej; Hoa, Neil T.; Akotia, Vimesh; Ma, Thomas Y.
CORPORATE SOURCE: Department of Medicine, DVA Medical Center, Long Beach, CA, USA
SOURCE: Life Sciences (2002), 70(25), 3029-3037
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Clin. studies indicate that specific cyclooxygenase-2 (Cox-2) inhibitors are less ulcerogenic than their non-selective predecessors (e.g. indomethacin). However, Cox-2 inhibitors may also interfere with ulcer healing. Re-epithelialization is a crucial factor in both gastrointestinal mucosal injury and ulcer healing. This study was aimed to compare the effects of selective Cox-2 inhibitor (**NS398**) vs. non-selective Cox inhibitor (indomethacin) on basal and basic fibroblast growth factor (bFGF) - stimulated gastric wound re-epithelialization. In-vitro epithelial wounds were created in confluent monolayers of RGM1 rat gastric epithelial cells by a razor blade scrape. Following wounding there was a significant re-epithelialization by 24 h. Indomethacin (0.25 mM and 0.5 mM) significantly inhibited basal wound re-epithelialization in a dose dependent manner. In contrast, selective Cox-2 inhibitor **NS398** did not inhibit the basal re-epithelialization process. Basic FGF **treatment** produced significant enhancement of **wound** re-epitheliazation at the various concns. [10, 20, 30, 40, 50 and 70 ng/mL] studied. Both indomethacin and **NS398** inhibited bFGF stimulated wound re-epithelialization, with indomethacin having a greater inhibitory effect. The extent of **NS398** inhibition was limited to the bFGF-stimulated component, whereas indomethacin inhibition extended to both the bFGF-stimulated and the basal re-epithelialization components. These findings indicate that specific Cox-2 inhibitor (**NS398**) does not interfere with the basal re-epithelialization but significantly inhibits the bFGF - stimulated re-epithelialization, whereas indomethacin interferes with both the basal as well as the bFGF-stimulated wound re-epithelialization.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:71904 HCAPLUS
DOCUMENT NUMBER: 136:112699
TITLE: Method of using cyclooxygenase 2 (COX-2) inhibitors in the treatment and prevention of ocular COX-2-mediated disorders
INVENTOR(S): Bandyopadhyay, Rebanta; Eveleth, David; Van Haarlem,

Tom; Kararli, Tugrul T.; Singh, Satish K.
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002005848	A2	20020124	WO 2001-US14600	20010504
WO 2002005848	A3	20020704		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-218101P P 20000713
US 2001-279285P P 20010328
OTHER SOURCE(S): MARPAT 136:112699
AB The invention provides methods for the treatment and prevention of ocular COX-2-mediated disorders using COX-2 inhibitors, e.g. **celecoxib**.
IT **162011-90-7**, Rofecoxib **169590-42-5**, **Celecoxib** **198470-84-7**, **Parecoxib**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase 2 inhibitors for treatment and prevention of ocular COX-2-mediated disorders)

L3 ANSWER 10 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:51982 HCAPLUS
DOCUMENT NUMBER: 136:96105
TITLE: Use of cox-2 inhibitors to **treat** **sepsis**, complications thereof, and pros EP receptor modulation
INVENTOR(S): Mack Strong, Vivian E.; Stapleton, Philip P.; Daly, John M.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 39 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002006915	A1	20020117	US 2001-782936	20010214

PRIORITY APPLN. INFO.: US 2000-182524P P 20000215
AB The present invention is directed to methods of preventing, inhibiting, reversing and/or ameliorating complications in those having or at risk for systemic inflammatory response syndrome, e.g., sepsis, including multiple organ dysfunction syndrome, pancreatitis, burns, trauma, and complications of sepsis such as bacteremia, pneumonia, urinary tract infections, wound infections, and drug reactions. The methods comprise administration of an

effective amt. of at least one of a selective inhibitor of cyclooxygenase-2, a drug which stimulates one or more PGE2 receptors or a drug which interferes with binding of PGE2 to one of more PGE2 receptors.

IT **123653-11-2, NS-398 162011-90-7, MK 0966 169590-42-5, Celecoxib 198470-84-7, Parecoxib**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of cox-2 inhibitors to **treat sepsis**, complications thereof, and prostaglandin EP receptor modulation)

L3 ANSWER 11 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:885859 HCAPLUS
DOCUMENT NUMBER: 136:632
TITLE: **Therapy** following skin **injury** from exposure to ultraviolet radiation
INVENTOR(S): Wilder, Karol J.; Schuh, Joseph R.
PATENT ASSIGNEE(S): Pharmacia Corp., USA
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001091856	A2	20011206	WO 2001-US17304	20010525
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
US 2002009421	A1	20020124	US 2001-866196	20010525

PRIORITY APPLN. INFO.: US 2000-208798P P 20000601
OTHER SOURCE(S): MARPAT 136:632

AB There is provided a method of relieving pain, fever and/or inflammation in a subject suffering sunburn or other skin injury resulting from exposure to UV radiation, the method comprising orally administering to the subject a therapeutically effective amt. of a selective COX-2 inhibitory drug. In an example provided a woman experienced no relief from sunburn after taking acetaminophen, but reported complete relief after taking Celebrex and reported a rapid healing of the burn with no blistering or peeling of surface skin.

IT **169590-42-5, Celecoxib**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapy with COX-2 inhibitors following skin injury from exposure to UV radiation)

IT **162011-90-7**, Rofecoxib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapy with COX-2 inhibitors following skin injury from exposure to UV radiation)

L3 ANSWER 12 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:694467 HCAPLUS
DOCUMENT NUMBER: 136:48008

TITLE: Selective inhibition of COX-2 improves early survival in murine endotoxemia but not in bacterial peritonitis
AUTHOR(S): Reddy, Raju C.; Chen, Gina H.; Tateda, Kazuhiro; Tsai, Wan C.; Phare, Susan M.; Mancuso, Peter; Peters-Golden, Marc; Standiford, Theodore J.
CORPORATE SOURCE: Division of Pulmonary and Critical Care Medicine, Department of Medicine, The University of Michigan Medical School, Ann Arbor, MI, 48109-0360, USA
SOURCE: American Journal of Physiology (2001), 281(3, Pt. 1), L537-L543
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Prostaglandins of the E series are believed to act as important mediators of several pathophysiol. events that occur in sepsis. Studies were performed to evaluate the effect of cyclooxygenase (COX)-2-specific inhibition on the outcome in murine endotoxemia and cecal ligation and puncture (CLP). We obsd. a significant time-dependent upregulation of PGE2 prodn. in both blood and lung homogenates of mice administered lipopolysaccharide i.p., which was nearly completely suppressed by the administration of the COX-2 inhibitor **NS-398**. Treatment with **NS-398** significantly improved early but not late survival in lipopolysaccharide-challenged mice. On the contrary, elevated PGE2 levels were found in bronchoalveolar lavage fluid but not in plasma of mice subjected to CLP (21 gauge). Pretreatment with **NS-398** failed to significantly improve survival in CLP mice. No significant differences were noted in plasma or lung homogenate proinflammatory cytokine levels or lung neutrophil sequestration between the **NS-398**-treated and control groups. These results demonstrate that selective COX-2 inhibition confers early but not long-term benefits without affecting the expression of proinflammatory cytokines or the development of lung inflammation.
IT **123653-11-2, NS-398**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective inhibition of COX-2 improves early survival in murine endotoxemia but not in bacterial peritonitis)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:616541 HCAPLUS
DOCUMENT NUMBER: 135:352454
TITLE: Cell cycle effects of nonsteroidal anti-inflammatory drugs and enhanced growth inhibition in combination with gemcitabine in pancreatic carcinoma cells
AUTHOR(S): Yip-Schneider, Michele T.; Sweeney, Christopher J.; Jung, Sin-Ho; Crowell, Pamela L.; Marshall, Mark S.
CORPORATE SOURCE: Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2001), 298(3), 976-985
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Increased cyclooxygenase-2 (COX-2) expression in human pancreatic adenocarcinomas, as well as the growth-inhibitory effect of nonsteroidal

anti-inflammatory drugs (NSAIDs) in vitro, suggests that NSAIDs may be an effective **treatment** for **pancreatic** cancer.
Gemcitabine is currently the most effective chemotherapeutic drug available for patients with pancreatic cancer, but is only minimally effective against this aggressive disease. Clearly, other treatment options must be identified. To design successful therapeutic strategies involving compds. either alone or in combination with others, it is necessary to understand their mechanism of action. In the present study, we evaluated the effects of three NSAIDs (sulindac, indomethacin, and **NS-398**) or gemcitabine in two human pancreatic carcinoma cell lines, BxPC-3 (COX-2-pos.) and PaCa-2 (COX-2-neg.), previously shown to be growth-inhibited by these NSAIDs. Effects on cell cycle and apoptosis were investigated by flow cytometry or Western blotting. Treatment with NSAIDs or gemcitabine altered the cell cycle phase distribution as well as the expression of multiple cell cycle regulatory proteins in both cell lines, but did not induce substantial levels of apoptosis. Furthermore, we demonstrated that the combination of the NSAID sulindac or **NS-398** with gemcitabine inhibited cell growth to a greater degree than either compd. alone. These results indicate that the antiproliferative effects of NSAIDs and gemcitabine in pancreatic tumor cells are primarily due to inhibition of cell cycle progression rather than direct induction of apoptotic cell death, regardless of COX-2 expression. In addn., NSAIDs in combination with gemcitabine may hold promise in the clinic for the **treatment** of **pancreatic** cancer.

IT **123653-11-2**, **NS-398**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cell cycle effects of NSAIDs and enhanced growth inhibition in combination with gemcitabine in pancreatic carcinoma cells)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:434854 HCAPLUS
DOCUMENT NUMBER: 135:51045
TITLE: Therapeutic compositions containing anti-inflammatory agents and biodegradable polyanhydrides
INVENTOR(S): Uhrich, Kathryn; Macedo, Braz
PATENT ASSIGNEE(S): Rutgers, the State University of New Jersey, USA; University of Medicine and Dentistry of New Jersey
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001041753	A2	20010614	WO 2000-US33378	20001207

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,

BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 1999-455861 A 19991207
AB Methods of promoting healing through enhanced regeneration of tissue (e.g. hard tissue or soft tissue) by contacting the tissue or the surrounding tissue with an antiinflammatory agent are useful in a variety of dental and orthopedic applications. Thus, poly[1,6-bis(o-carboxyphenoxy)hexane] was prepd. in a series of steps by the treatment of salicylic acid with 1,6-dibromohexane, and polymn. of the resulting 1,6-bis(o-carboxyphenoxy)hexane. The polymer was characterized by glass transition temp. measurements and then subjected to compression molding.
IT **162011-90-7**, Rofecoxib **169590-42-5**, Celebrex
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic compns. contg. antiinflammatory agents and biodegradable polyanhydrides)

L3 ANSWER 15 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:380397 HCAPLUS
DOCUMENT NUMBER: 135:488
TITLE: Use of NSAIDs for the **treatment** of **pancreatic** cancer
INVENTOR(S): Marshall, Mark Steven; Sweeney, Christopher J.; Yip-schneider, Michelle T.; Crowell, Pamela L.
PATENT ASSIGNEE(S): Advanced Research and Technology Institute, Inc., USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001035956	A1	20010525	WO 2000-US31410	20001115
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1229908	A1	20020814	EP 2000-980405	20001115
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 1999-165543P P 19991115
WO 2000-US31410 W 20001115
AB The invention provides a method comprising the use of non-steroidal antiinflammatory drugs (NSAIDs), preferably a COX-2 inhibitor, particularly sulindac or its analogs to **treat pancreatic** cancer. Also provided is a method of increasing susceptibility of pancreatic cancer cells to chemotherapeutic agents comprising contacting the cells with an effective sensitizing amt. of an NSAID. The synergistic effect of a combination of sulindac and gemcitabine is demonstrated. Cox-2 expression in pancreatic adenocarcinomas was detd.
IT **123653-11-2, NS-398**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sulindac or other NSAID for **pancreatic** cancer

treatment, and chemotherapeutic agent sensitization method)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 16 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:365798 HCAPLUS
DOCUMENT NUMBER: 136:210208
TITLE: **NS-398 Treatment** after **Trauma** Modifies NF-.kappa.B Activation and Improves Survival
AUTHOR(S): Mack Strong, V. E.; Mackrell, P. J.; Concannon, E. M.; Mestre, J. R.; Smyth, Gordon P.; Schaefer, P. A.; Stapleton, P. P.; Daly, J. M.
CORPORATE SOURCE: New York Presbyterian Hospital-Weill Medical College of Cornell University, New York, NY, USA
SOURCE: Journal of Surgical Research (2001), 98(1), 40-46
CODEN: JSGRA2; ISSN: 0022-4804
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Prostaglandin E2 (PGE2) prodn. after trauma contributes to immune alterations that increase susceptibility to infections. We hypothesize that blocking PGE2 with **NS-398**, a selective COX-2 inhibitor, will modulate this response and improve outcome. This study evaluated the effect of **NS-398** given over 7 days on proinflammatory cytokines, intracellular signaling, and survival after a septic challenge. Balb/C mice (n = 8/group) were given 10 mg/kg **NS-398** i.p. over 7 days, starting after anesthesia or trauma (femur fracture + 40% hemorrhage). Four groups, anesthesia + vehicle (C), anesthesia + **NS-398** (CN), trauma + vehicle (T), or trauma + **NS-398** (TN), were studied. On Day 7 after trauma, mice were sacrificed, serum was collected, and splenic macrophages were evaluated for PGE2, LTB4, IL-6, TNF-.alpha., and NO prodn. Addnl., macrophage COX-2 mRNA, I.kappa.B-.alpha., and NF-.kappa.B were evaluated. In a sep. study, mice (n = 10-11/group) were traumatized and given **NS-398** over 7 days, and then cecal ligation and puncture (CLP) were performed. Mice were then followed for survival over 10 days (via log-rank test). **NS-398** **treatment** of **injured** mice decreased PGE prodn. compared to T (3.90.3 vs. 3.10.4 pg/g protein), and significantly decreased IL-6, NO, and TNF- prodn. **NS-398** treatment also attenuated COX-2 mRNA levels and NF-.kappa.B activation. These cellular events correlate with a significant survival advantage in TN vs. T mice after CLP. These data suggest that a specific COX-2 inhibitor not only suppresses PGE, but normalizes proinflammatory cytokines after trauma through changes that may partly be mediated via transcriptional events. This correlates with significantly increased survival in TN mice given a septic challenge and suggests that COX-2 inhibitors contribute to modulating the inflammatory response and improving survival after trauma. (c) 2001 Academic Press.
IT **123653-11-2, NS-398**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**NS-398 treatment** after **trauma** modifies NF-.kappa.B activation and improves survival)
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 17 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:282229 HCAPLUS

DOCUMENT NUMBER: 135:86770
TITLE: Effects of specific inhibition of cyclo-oxygenase-1 and cyclo-oxygenase-2 in the rat stomach with normal mucosa and after acid challenge
AUTHOR(S): Gretzer, Britta; Maricic, Nenad; Respondek, Michael; Schuligoi, Rufina; Peskar, Brigitta M.
CORPORATE SOURCE: Department of Experimental Clinical Medicine, Ruhr-University of Bochum, Bochum, D-44780, Germany
SOURCE: British Journal of Pharmacology (2001), 132(7), 1565-1573
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 1 Effects of the cyclo-oxygenase (COX)-1 inhibitor SC-560 and the COX-2 inhibitors rofecoxib and DFU were investigated in the normal stomach and after acid challenge. In healthy rats, neither SC-560 nor rofecoxib (20 mg kg-1 each) given alone damaged the mucosa. Co-treatment with SC-560 and rofecoxib, however, induced severe lesions comparable to indomethacin (20 mg kg-1) whereas co-administration of SC-560 and DFU (20 mg kg-1 each) had no comparable ulcerogenic effect 5 h after dosing. SC-560 (20 mg kg-1) inhibited gastric 6-keto-prostaglandin (PG) F1.alpha. by 86.+-.5% and platelet thromboxane (TX) B2 formation by 89.+-.4% comparable to indomethacin (20 mg kg-1). Rofecoxib (20 mg kg-1) did not inhibit gastric and platelet eicosanoids. Intragastric HCl elevated mucosal mRNA levels of COX-2 but not COX-1. Dexamethasone (2 mg kg-1) prevented the up-regulation of COX-2. After acid challenge, SC-560 (5 and 20 mg kg-1) induced dose-dependent injury. Rofecoxib (20 mg kg-1), DFU (5 mg kg-1) and dexamethasone (2 mg kg-1) given alone were not ulcerogenic but aggravated SC-560-induced damage. DFU augmented SC-560 damage 1 but not 5 h after administration whereas rofecoxib increased **injury** after both **treatment** periods suggesting different time courses. Gastric injurious effects of rofecoxib and DFU correlated with inhibition of inflammatory PGE2. The findings show that in the normal stomach lesions only develop when both COX-1 and COX-2 are inhibited. In contrast, during acid challenge inhibition of COX-1 renders the mucosa more vulnerable suggesting an important role of COX-1 in mucosal defense in the presence of a potentially noxious agent. In this function COX-1 is supported by COX-2. In the face of pending injury, however, COX-2 cannot maintain mucosal integrity when the activity of COX-1 is suppressed.
IT **162011-90-7**, Rofecoxib
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(COX-1 and COX-2 inhibition effect in stomach with normal mucosa and after acid challenge)
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 18 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:861523 HCAPLUS
DOCUMENT NUMBER: 134:32985
TITLE: Pharmaceutical transdermal compositions
INVENTOR(S): Ragavan, Vanaja V.
PATENT ASSIGNEE(S): Aviana Biopharm, USA
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000072883	A2	20001207	WO 2000-US15289	20000602

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-137186P P 19990602

AB The compns. allow for the delivery of substances to the organs of the skin such as hair follicles and sebaceous glands, to the tissues under the skin such as muscles, joints and related tissues and to the systemic circulation. The compns. can be used to treat a variety of skin disorders as well as disorders of deeper tissue or disorder distant to the site of application through absorption through the skin. The formulations include pharmaceutical compns. with or without enhancers for delivery of active ingredients to the skin and organs of the skin to treat common disorders of the skin and its organs, as well as areas distant from the skin, i.e., regional or systemic delivery via transdermal administration. Preferred enhancers combine a diol and a cell-envelope disrupting agent. Examples of dermatol. conditions which can be treated include sunburn prevention and **treatment**, minor and major **burns**, agents toxic to the skin such as poison ivy, chem. and non-chem. such as radiation that disrupt the normal epidermis, conditions of the skin organs such as hirsutism, acne, infections such as bacterial and viral infection, inflammatory processes such as after application of facial peels, lasers, tanning agents, drug reactions, muscular and joint inflammation and pain such as arthritis and sports injuries, hormone deficiencies, menopause, and contraception. Examples were given showing the effectiveness of an enhancer (oleic acid) in flutamide or ibuprofen skin penetration.

IT **162011-90-7**, Rofecoxib **169590-42-5**, **Celecoxib**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(transdermal pharmaceutical compns. contg. skin penetration enhancers)

L3 ANSWER 19 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:595069 HCAPLUS
DOCUMENT NUMBER: 134:51091
TITLE: Blockade of cyclooxygenase-2 inhibits proliferation and induces apoptosis in human pancreatic cancer cells
AUTHOR(S): Ding, Xian-Zhong; Tong, Wei-Gang; Adrian, Thomas E.
CORPORATE SOURCE: Department of Biomedical Sciences, Creighton University School of Medicine, Omaha, NE, 68178, USA
SOURCE: Anticancer Research (2000), 20(4), 2625-2631
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclooxygenase (COX), also referred to as prostaglandin endoperoxide synthase, is a key enzyme in the conversion of arachidonic acid to prostaglandins and other eicosanoids. Epidemiol., animal and in vitro observations show a pos. correlation between the expression of COX (esp. COX- 2) and colonic cancer development, growth and apoptosis. Constitutive expression of COX-2 in human pancreatic cancer cells was recently reported. To evaluate the potential role of COX in pancreatic cancer, RT-PCR was used to det. the constitutive expression of COX-2 in four pancreatic cancer cell lines, MiaPaCa2, PANC-1, HPAF, ASPC- 1. The

effect of COX blockade with either the general COX inhibitor, indomethacin, or the specific COX-2 inhibitor, **NS-398**, on [3H]-thymidine incorporation and cell no. was investigated in these four pancreatic cancer cell lines. In addn., the effects of these COX inhibitors on pancreatic cancer cell apoptosis was evaluated by DNA propidium iodide staining and the terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL) assay. All four human pancreatic cancer cell lines expressed COX-2 and their proliferation was concn.- and time-dependently inhibited by both indomethacin and **NS398**. Substantial apoptosis was also induced by **treatment** of **pancreatic** cancer cells with either indomethacin or **NS398**, as indicated by both DNA propidium iodide staining and the TUNEL assay. Furthermore, indomethacin and **NS398** were equipotent for growth inhibition and induction of apoptosis, indicating that eicosanoid synthesis via COX-2 is involved in pancreatic cancer cell proliferation and survival. In conclusion, these findings suggest that the COX pathway, esp. COX-2, contributes to the growth and apoptosis of pancreatic cancer. Specific COX-2 inhibitors are likely to be valuable for the treatment and prevention of this deadly cancer.

IT **123653-11-2, NS-398**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blockade of cyclooxygenase-2 inhibits proliferation and induces apoptosis in human pancreatic cancer cells)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 20 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:171920 HCAPLUS
DOCUMENT NUMBER: 132:317766
TITLE: Wound collagen deposition in rats: effects of an NO-NSAID and a selective COX-2 inhibitor
AUTHOR(S): Muscara, Marcelo N.; McKnight, Webb; Asfaha, Samuel; Wallace, John L.
CORPORATE SOURCE: Department of Pharmacology & Therapeutics, University of Calgary, Calgary, AB, T2N 4N1, Can.
SOURCE: British Journal of Pharmacology (2000), 129(4), 681-686
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 1 Selective cyclo-oxygenase (COX)-2 inhibitors and nitric oxide-releasing nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit reduced toxicity in the gastrointestinal tract, but may affect wound healing in other tissues. In this study, we have compared the effects of a selective COX-2 inhibitor (**celecoxib**), a nitric-oxide releasing deriv. of naproxen (HCT-3012) and naproxen in a model of wound collagen deposition in the rat. 2 Polyvinyl alc. sponges were implanted s.c. in rats. The rats were treated daily for 5 days with the test drugs at equieffective anti-inflammatory doses. 3 Naproxen (10 mg kg-1) significantly decreased (45%) collagen deposition at the **wound** site relative to the vehicle-**treated** control group. In contrast, HCT-3012 (14.5 mg kg-1) significantly increased (62%) collagen deposition, while **celecoxib** (10 mg kg-1) had no effect. 4 Naproxen and HCT-3012 suppressed prostaglandin (PG) E2 levels at the wound site and whole blood thromboxane synthesis to similar degrees. **Celecoxib** had no significant effect on wound fluid PGE2 levels, but slightly reduced whole blood thromboxane synthesis (by 17%). 5 COX-1 mRNA and protein were

expressed in the wound exudate, the skin surrounding the wound and in normal skin. In contrast, COX-2 mRNA, but not protein, was expressed in wound and normal skin. 6 These results demonstrate that HCT-3012 can significantly enhance collagen deposition at a wound site, despite inhibiting prostaglandin synthesis to the same extent as the parent drug. Nitric oxide-releasing NSAIDs may represent a safer alternative to std. NSAIDs for use as anti-inflammatory and analgesic agents by post-surgery patients.

IT **169590-42-5, Celecoxib**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of nitric oxide-NSAID vs. a selective COX-2 inhibitor on wound collagen deposition in rats)

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 21 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:160069 HCAPLUS
DOCUMENT NUMBER: 132:291951
TITLE: Cyclooxygenase-2 expression in human pancreatic adenocarcinomas
AUTHOR(S): Yip-Schneider, Michele T.; Barnard, Darlene S.; Billings, Steven D.; Cheng, Liang; Heilman, Douglas K.; Lin, Amy; Marshall, Steven J.; Crowell, Pamela L.; Marshall, Mark S.; Sweeney, Christopher J.
CORPORATE SOURCE: Department of Medicine, Department of Biochemistry and Walther Oncology Center Indiana University School of Medicine, Indiana University-Purdue University, Indianapolis, IN, 46202, USA
SOURCE: Carcinogenesis (2000), 21(2), 139-146
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclooxygenase-2 (COX-2) expression is up-regulated in several types of human cancers and has also been directly linked to carcinogenesis. To investigate the role of COX-2 in pancreatic cancer, we evaluated COX-2 protein expression in primary human pancreatic adenocarcinomas (n = 23) and matched normal adjacent tissue (n = 11) by immunoblot anal. COX-2 expression was found to be significantly elevated in the pancreatic tumor specimens compared with normal pancreatic tissue. To examine whether the elevated levels of COX-2 protein obsd. in pancreatic tumors correlated with the presence of oncogenic K-ras, we detd. the K-ras mutation status in a subset of the tumors and corresponding normal tissues. The presence of oncogenic K-ras did not correlate with the level of COX-2 protein expressed in the pancreatic adenocarcinomas analyzed. These observations were also confirmed in a panel of human pancreatic tumor cell lines. Furthermore, in the pancreatic tumor cell line expressing the highest level of COX-2 (BxPC-3), COX-2 expression was demonstrated to be independent of Erk1/2 activation. The lack of correlation between COX-2 and oncogenic K-ras expression suggests that Ras activation may not be sufficient to induce COX-2 expression in pancreatic tumor cells and that the aberrant activation of signaling pathways other than Ras may be required for up-regulating COX-2 expression. We also report that the COX inhibitors sulindac, indomethacin and **NS-398** inhibit cell growth in both COX-2-pos. (BxPC-3) and COX-2-neg. (PaCa-2) pancreatic tumor cell lines. However, suppression of cell growth by indomethacin and **NS-398** was significantly greater in the BxPC-3 cell line compared with the PaCa-2 cell line ($P = 0.004$ and $P < 0.001$, resp.). In

addn., the three COX inhibitors reduce prostaglandin E2 levels in the BxPC-3 cell line. Taken together, our data suggest that COX-2 may play an important role in pancreatic tumorigenesis and therefore be a promising chemotherapeutic target for the **treatment** of **pancreatic** cancer.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 22 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:580522 HCAPLUS
DOCUMENT NUMBER: 131:295241
TITLE: Increased cyclooxygenase-2 expression in human pancreatic carcinomas and cell lines: growth inhibition by nonsteroidal anti-inflammatory drugs
AUTHOR(S): Molina, Miguel A.; Sitja-Arnau, Marta; Lemoine, Michael G.; Frazier, Marsha L.; Sinicrope, Frank A.
CORPORATE SOURCE: Department of Epidemiology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Cancer Research (1999), 59(17), 4356-4362
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclooxygenase (COX)-2 mRNA and protein expression were frequently elevated in human pancreatic adenocarcinomas and cell lines derived from such tumors. Immunohistochem. demonstrated cytoplasmic COX-2 expression in 14 of 21 (67%) pancreatic carcinomas. The level of COX-2 mRNA was elevated in carcinomas, relative to histol. normal pancreas from a healthy individual, as assessed by reverse transcription-PCR. COX-2 protein expression was detected by the Western blot assay in three of five pancreatic carcinoma cell lines (BxPC-3, Capan-1, and MDAPanc-3), whereas COX-1 protein was detected in two of the five cell lines (BxPC-3 and Capan-1). Increased levels of COX-2 mRNA were found in four of five cell lines, and only in PANC-1 cells was the low level of transcript comparable to that in the normal pancreas. The level of COX-2 mRNA was pos. correlated with the differentiation status of the tumor of origin for each cell line, COX-2 protein expression was up-regulated by epidermal growth factor when the cells were grown in absence of serum. Finally, two nonsteroidal anti-inflammatory drugs, sulindac sulfide and **NS398**, produced a dose-dependent inhibition of cell proliferation in all pancreatic cell lines tested. No correlation was found between the level of COX-2 or COX-1 expression and the extent of growth inhibition. Treatment of BxPC-3 cells with sulindac sulfide and **NS398** resulted in an induction of COX-2 expression. The authors findings indicate that COX-2 up-regulation is a frequent event in pancreatic cancers and suggest that nonsteroidal anti-inflammatory drugs may be useful in the chemoprevention and **therapy** of **pancreatic** carcinoma.

IT **123653-11-2, NS398**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(increased cyclooxygenase-2 expression in human pancreatic carcinomas and cell lines and growth inhibition by nonsteroidal anti-inflammatory drugs in relation to up-regulation by epidermal growth factor)

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 23 OF 23 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:575527 HCAPLUS

DOCUMENT NUMBER: 129:310592
TITLE: Cyclooxygenase-2 inhibitor **NS-398** improves survival and restores leukocyte counts in burn infection
AUTHOR(S): Shoup, Margo; He, Li-Ke; Liu, Hong; Shankar, Ravi; Gamelli, Richard
CORPORATE SOURCE: Loyola University Medical Center, Burn and Shock Trauma Institute and the Department of Surgery, Maywood, IL, 60153, USA
SOURCE: Journal of Trauma: Injury, Infection, and Critical Care (1998), 45(2), 215-221
CODEN: JOTRFA; ISSN: 1079-6061
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclooxygenase-2 (COX-2) is a key enzyme in the prodn. of prostaglandin E2 (PGE2) from activated macrophages. PGE2 is increased during trauma and sepsis and has been implicated as a neg. immunomodulator. The objective of this study was to det. the therapeutic benefits of a COX-2 inhibitor (**NS-398**) on survival and leukocyte prodn. in a murine model of burn sepsis. To det. the in vitro ability of **NS-398** to inhibit macrophage prodn. of PGE2, peritoneal elicited macrophages were stimulated for 18 h with medium alone, endotoxin (ETX) (1 .mu.mol/L), or ETX plus **NS-398** (0.3 .mu.mol/L). Macrophage supernatant PGE2 levels were detd. by an enzyme immunoassay. To test the in vivo efficacy of **NS-398**, mice subjected to a 15% dorsal scald burn plus 1,000 colony-forming units of topical Pseudomonas aeruginosa received either 10 mg/kg **NS-398** i.p. or placebo 4 to 6 h after infection and twice daily for 3 days. Survival was measured up to 14 days, and circulating white blood cell (WBC) count and abs. neutrophil count (ANC) were detd. 3 days after injury. Macrophage PGE2 prodn. was significantly increased in the ETX-treated group compared with the medium-alone group, and this increase was completely normalized with the addn. of **NS-398**. **NS-398** also augmented WBC count (4,288.+-.649 vs. 7,866.+-.435 per mm3; $p < 0.01$) and ANC (1,068.+-.255 vs. 3,663.+-.474 per mm3) after burn infection and attenuated macrophage depression of hematopoietic proliferation. Finally, **NS-398** **treatment** significantly improved survival after **burn** infection, from 0 to 45.5%. Inhibition of the COX-2 isoform of cyclooxygenase with **NS-398** inhibited macrophage PGE2 prodn., restored ANC, and improved survival during burn infection. **NS-398**, therefore, has potential therapeutic benefits in septic patients who have developed neutropenia.

IT **123653-11-2, NS-398**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cyclooxygenase-2 inhibitor **NS-398** improves survival and restores leukocyte counts in murine model of burn infection)

FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO' ENTERED AT 16:33:29 ON 03 SEP 2002
L4 70 SEA ABB=ON PLU=ON L3
L5 42 DUP REMOVE L4 (28 DUPLICATES REMOVED)

=> d ibib abs l5 1-42

L5 ANSWER 1 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:374939 BIOSIS

DOCUMENT NUMBER: PREV200200374939
TITLE: Author's responses.
AUTHOR(S): Dahners, Laurence E. (1)
CORPORATE SOURCE: (1) Chapel Hill, NC USA
SOURCE: American Journal of Sports Medicine, (May June, 2002) Vol. 30, No. 3, pp. 457. print.
ISSN: 0363-5465.
DOCUMENT TYPE: Letter
LANGUAGE: English

L5 ANSWER 2 OF 42 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002389102 MEDLINE
DOCUMENT NUMBER: 22133545 PubMed ID: 12138016
TITLE: NSAID inhibition of RGM1 gastric monolayer wound re-epithelialization: comparison of selective Cox-2 versus non-selective Cox inhibitors.
AUTHOR: Giap Andrew Q; Tarnawski Andrzej; Hoa Neil T; Akotia Vimesh; Ma Thomas Y
CORPORATE SOURCE: Department of Medicine, DVA Medical Center, Long Beach, CA, USA.
SOURCE: LIFE SCIENCES, (2002 May 10) 70 (25) 3029-37.
Journal code: 0375521. ISSN: 0024-3205.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020725
Last Updated on STN: 20020820
Entered Medline: 20020819

AB Clinical studies indicate that specific cyclooxygenase-2 (Cox-2) inhibitors are less ulcerogenic than their non-selective predecessors (e.g. indomethacin). However, Cox-2 inhibitors may also interfere with ulcer healing. Re-epithelialization is a crucial factor in both gastrointestinal mucosal injury and ulcer healing. This study was aimed to compare the effects of selective Cox-2 inhibitor (**NS398**) versus non-selective Cox inhibitor (indomethacin) on basal and basic fibroblast growth factor (bFGF) - stimulated gastric wound re-epithelialization. In-vitro epithelial wounds were created in confluent monolayers of RGM1 rat gastric epithelial cells by a razor blade scrape. Following wounding there was a significant re-epithelialization by 24 hrs. Indomethacin (0.25 mM and 0.5 mM) significantly inhibited basal wound re-epithelialization in a dose dependent manner. In contrast, selective Cox-2 inhibitor **NS398** did not inhibit the basal re-epithelialization process. Basic FGF **treatment** produced significant enhancement of **wound** re-epitheliazation at the various concentrations [10, 20, 30, 40, 50 and 70 ng/ml] studied. Both indomethacin and **NS398** inhibited bFGF stimulated wound re-epithelialization, with indomethacin having a greater inhibitory effect. The extent of **NS398** inhibition was limited to the bFGF-stimulated component, whereas indomethacin inhibition extended to both the bFGF-stimulated and the basal re-epithelialization components. These findings indicate that specific Cox-2 inhibitor (**NS398**) does not interfere with the basal re-epithelialization but significantly inhibits the bFGF - stimulated re-epithelialization, whereas indomethacin interferes with both the basal as well as the bFGF-stimulated wound re-epithelialization.

L5 ANSWER 3 OF 42 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002145463 EMBASE
TITLE: Inhibition of Helicobacter pylori-induced cyclo-oxygenase-2

aggravates NSAID-caused gastric damage in Mongolian gerbils.

AUTHOR: Futacam S.; Hiratsuka T.; Wada K.; Tatsuguchi A.; Tsukui T.; Miyake K.; Akamatsu T.; Hosone M.; Sakamoto C.; Kobayashi M.

CORPORATE SOURCE: Dr. C. Sakamoto, Third Dept. of Internal Medicine, Nippott Medical School, 1-1-5, Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan. choitsu@nms.ac.jp

SOURCE: Alimentary Pharmacology and Therapeutics, (2002) 16/4 (847-855).
Refs: 35
ISSN: 0269-2813 CODEN: APTHEN

COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology

LANGUAGE: English
SUMMARY LANGUAGE: English

AB The effect of Helicobacter pylori infection on non-steroidal anti-inflammatory drug-induced gastric mucosal injury is controversial. Aim: To examine the effect of the interaction between H. pylori and non-steroidal anti-inflammatory drugs on gastric mucosal injury. Methods: Mongolian gerbils infected with H. pylori were treated with indometacin at 8 mg/kg for 2 days or 7 days. Mucosal damage was assessed by macroscopic and histological examination, and myeloperoxidase activity was measured as an index of neutrophil infiltration. The expression levels of cyclo-oxygenase proteins were determined by Western blot analysis and cyclo-oxygenase activity. Results: A 2-day course of indometacin did not cause an increase in gastric damage in H. pylori infected Mongolian gerbils compared to uninfected gerbils, while a 7-day course of indometacin caused additive gastric damage in H. pylori-infected animals. H. pylori infection induced cyclo-oxygenase-2 expression in the stomach. Treatment with indometacin for 2 days did not significantly affect cyclo-oxygenase activity in H. pylori infected animals, while treatment for 7 days inhibited both cyclo-oxygenase-1 and cyclo-oxygenase-2 activities. Pre-treatment with a selective cyclo-oxygenase-2 inhibitor aggravated mucosal **injury** in H. pylori-infected animals **treated** or not treated with indometacin for 2 days. Conclusions: Our results suggest that cyclo-oxygenase2 protein induced by H. pylori infection may be involved in the defence of the gastric mucosa against damage caused by non-steroidal anti-inflammatory drugs. Therefore, inhibition of cyclo-oxygenase-2 activity may enhance non-steroidal anti-inflammatory drug-caused gastric damage in H. pylori-infected animals.

L5 ANSWER 4 OF 42 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 2002241677 MEDLINE
DOCUMENT NUMBER: 21947758 PubMed ID: 11950805

TITLE: Recovery of ischaemic injured porcine ileum: evidence for a contributory role of COX-1 and COX-2.

AUTHOR: Blikslager A T; Zimmel D N; Young K M; Campbell N B; Little D; Argenzio R A

CORPORATE SOURCE: Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina 27606, USA.. Anthony_Blikslager@ncsu.edu

CONTRACT NUMBER: DK34987 (NIDDK)
DK53284 (NIDDK)
SOURCE: GUT, (2002 May) 50 (5) 615-23.

Journal code: 2985108R. ISSN: 0017-5749.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020501
Last Updated on STN: 20020604
Entered Medline: 20020603

AB BACKGROUND: We have previously shown that the non-selective cyclooxygenase (COX) inhibitor indomethacin retards recovery of intestinal barrier function in ischaemic injured porcine ileum. However, the relative role of COX-1 and COX-2 elaborated prostaglandins in this process is unclear. AIMS: To assess the role of COX-1 and COX-2 elaborated prostaglandins in the recovery of intestinal barrier function by evaluating the effects of selective COX-1 and COX-2 inhibitors on mucosal recovery and eicosanoid production. METHODS: Porcine ileal mucosa subjected to 45 minutes of ischaemia was mounted in Ussing chambers, and transepithelial electrical resistance was used as an indicator of mucosal recovery. Prostaglandins E1 and E2 (PGE) and 6-keto-PGF1alpha (the stable metabolite of prostaglandin I2 (PGI2)) were measured using ELISA. Thromboxane B2 (TXB2, the stable metabolite of TXA2) was measured as a likely indicator of COX-1 activity. RESULTS: Ischaemic injured tissues recovered to control levels of resistance within three hours whereas tissues treated with indomethacin (5x10(-6) M) failed to fully recover, associated with inhibition of eicosanoid production. **Injured** tissues **treated** with the selective COX-1 inhibitor SC-560 (5x10(-6) M) or the COX-2 inhibitor **NS-398** (5x10(-6) M) recovered to control levels of resistance within three hours, associated with significant elevations of PGE and 6-keto-PGF1alpha compared with untreated tissues. However, SC-560 significantly inhibited TXB2 production whereas **NS-398** had no effect on this eicosanoid, indicating differential actions of these inhibitors related to their COX selectivity. CONCLUSIONS: The results suggest that recovery of resistance is triggered by PGE and PGI2, which may be elaborated by either COX-1 or COX-2.

L5 ANSWER 5 OF 42 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2002350462 IN-PROCESS
DOCUMENT NUMBER: 22088261 PubMed ID: 12093311
TITLE: Renal failure associated with the use of **celecoxib** and rofecoxib.
AUTHOR: Ahmad Syed R; Kortepeter Cindy; Brinker Allen; Chen Min; Beitz Julie
CORPORATE SOURCE: Division of Drug Risk Evaluation, Office of Drug Safety, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland, USA.
SOURCE: DRUG SAFETY, (2002) 25 (7) 537-44.
Journal code: 9002928. ISSN: 0114-5916.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020703
Last Updated on STN: 20020703

AB OBJECTIVE: **Celecoxib** and rofecoxib are two relatively new nonsteroidal anti-inflammatory drugs (NSAIDs) that selectively inhibit the cyclo-oxygenase-2 (COX-2) isoenzyme at therapeutic concentrations. The nephrotoxic potential of selective COX-2 inhibitors has not been clearly established. This study was conducted in order to understand the association between acute renal failure and the two COX-2 inhibitors

celecoxib and rofecoxib. METHODS: A search was performed in the US Food and Drug Administration's (FDA) Adverse Event Reporting System (AERS) to identify cases of renal failure submitted to the FDA. A MEDLINE search of the English language literature was also performed to identify published cases of renal failure associated with **celecoxib** and rofecoxib. RESULTS: One hundred twenty-two and 142 domestic US cases of **celecoxib** and rofecoxib-associated renal failure, respectively, were identified in the AERS database. The literature search identified 19 cases of acute renal impairment in association with **celecoxib** and rofecoxib. In addition, drug regulatory authorities in the UK, Canada, and Australia have received about 50 reports of renal failure with **celecoxib** and rofecoxib. Descriptive statistics of the AERS cases have been summarised in this report. CONCLUSIONS: Data from AERS and published case reports suggest that use of both these drugs is associated with renal effects similar to that of conventional nonselective NSAIDs. Physicians should be aware that serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short-term therapy with **celecoxib** and rofecoxib. Patients at greatest risk for renal injury are those with pre-existing renal impairment, heart failure, liver dysfunction, those taking diuretics and/or ACE inhibitors, and the elderly. Kidney function should be monitored closely for any signs of potential renal **injuries** soon after initiating **treatment** with these agents, especially in high-risk populations. In addition, healthcare practitioners should adequately warn patients of the signs and symptoms of serious renal toxicity, and of the need for them to see their physician promptly if they occur. **Celecoxib** and rofecoxib are not recommended for use in patients with advanced renal disease.

L5 ANSWER 6 OF 42 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002187363 EMBASE
TITLE: Fever: Beneficial and detrimental effects of antipyretics.
AUTHOR: Greisman L.A.; Mackowiak P.A.
CORPORATE SOURCE: Dr. P.A. Mackowiak, Medical Service, Veterans Affairs Medical Center, 10 N. Greene Street, Baltimore, MD 21201, United States. philip.mackowiak@med.va.gov
SOURCE: Current Opinion in Infectious Diseases, (2002) 15/3 (241-245).
Refs: 57
ISSN: 0951-7375 CODEN: COIDE5
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Although various forms of therapy have been used, since antiquity, to lower the temperature of febrile patients, it is still not known whether the benefits of antipyretic therapy outweigh its risks. Justifications for the use of antipyretic drugs, and the evidence pertaining to these rationales, are examined. Antipyretic **therapy** in **sepsis** , and adverse effects of antipyretic medications, are also reviewed. .COPYRGT. 2002 Lippincott Williams & Wilkins.

L5 ANSWER 7 OF 42 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002110206 EMBASE
TITLE: Treatment of pain in acutely burned children.
AUTHOR: Stoddard F.J.; Sheridan R.L.; Saxe G.N.; King B.S.; King B.H.; Chedekel D.S.; Schnitzer J.J.; Martyn J.A.J.
SOURCE: Journal of Burn Care and Rehabilitation, (2002) 23/2

(135-156).
Refs: 200
ISSN: 0273-8481 CODEN: JBCRD2
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
009 Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The child with burns suffers severe pain at the time of the **burn** and during subsequent **treatment** and rehabilitation. Pain has adverse physiological and emotional effects, and research suggests that pain management is an important factor in better outcomes. There is increasing understanding of the private experience of pain, and how children benefit from honest preparation for procedures. Developmentally appropriate and culturally sensitive pain assessment, pain relief, and reevaluation have improved, becoming essential in treatment. Pharmacological treatment is primary, strengthened by new concepts from neurobiology, clinical science, and the introduction of more effective drugs with fewer adverse side effects and less toxicity. Empirical evaluation of various hypnotic, cognitive, behavioral, and sensory treatment methods is advancing. Multidisciplinary assessment helps to integrate psychological and pharmacological pain-relieving interventions to reduce emotional and mental stress, and family stress as well. Optimal care encourages burn teams to integrate pain guidelines into protocols and critical pathways for improved care.

L5 ANSWER 8 OF 42 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002148562 EMBASE
TITLE: Projecting future drug expenditures - 2002.
AUTHOR: Shah N.D.; Vermeulen L.C.; Santell J.P.; Hunkler R.J.; Hontz K.
CORPORATE SOURCE: L.C. Vermeulen, Univ. of Wisconsin Hospital/Clinics, 100 Highland Avenue, Madison, WI 53792, United States
SOURCE: American Journal of Health-System Pharmacy, (15 Jan 2002) 59/2 (131-142).
Refs: 30
ISSN: 1079-2082 CODEN: AHSPEK
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 036 Health Policy, Economics and Management
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Drug-cost projections for 2002 and factors likely to influence drug costs are discussed. The United States continues to face the challenge of increased growth in health expenditures, and pharmaceutical expenditures continue to increase significantly faster than the growth in total health care expenditures. These increases can be largely attributed to a combination of general inflation, an increase in the average age of the U.S. population, and the increased use of new technologies. On the basis of price inflation and nonprice inflationary factors, including increases in volume, shifts in patient and therapeutic intensity, and the expected approval of new drugs, we forecast a 15.5% increase in drug expenditures in 2002 for hospitals and clinics and an 18.5% increase for ambulatory care settings. One of the most substantial contributors to the rise in pharmaceutical expenditures over the past decade is the successful

introduction and rapid diffusion of new pharmaceuticals. Data about many new drugs on the horizon are provided. One agent likely to have the highest impact on hospitals in the next year is drotrecogin alfa for the **treatment** of **sepsis**. The cost of this agent is expected to range from $3,000 to $10,000 per patient per course of therapy. Other factors influencing medication costs, including generic medications, legislative initiatives, and the recent acts of terrorism committed against the United States, are also discussed. Technological, demographic, and market-based changes, and possibly public policy changes, will have a dramatic influence on pharmaceutical expenditures in the coming year. An understanding of what is driving the changes is critical to the effective management of these resources.

L5 ANSWER 9 OF 42 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2002367453 MEDLINE
DOCUMENT NUMBER: 22015338 PubMed ID: 12020867
TITLE: Role for both spinal cord COX-1 and COX-2 in maintenance of mechanical hypersensitivity following peripheral nerve injury.
AUTHOR: Ma Weiya; Du Wei; Eisenach James C
CORPORATE SOURCE: Pain Mechanisms Laboratory, Department of Anesthesiology and Center for the Study of Pharmacologic Plasticity in the Presence of Pain, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1009, USA.. wma@wfubmc.edu
CONTRACT NUMBER: GM48085 (NIGMS)
NS41386 (NINDS)
SOURCE: BRAIN RESEARCH, (2002 May 24) 937 (1-2) 94-9.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020713
Last Updated on STN: 20020814
Entered Medline: 20020813

AB The effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) in **treating** neuropathic pain caused by nerve **injury** has been controversial. In the present study, 4 weeks following partial sciatic nerve ligation, a single intrathecal injection of the cyclooxygenase (COX)-1 preferring inhibitor ketorolac (50 microg) significantly attenuated tactile allodynia for 6 days. The COX-2 preferring inhibitor, **NS-398** (60 microg) significantly reversed tactile allodynia 2 h following injection but this anti-allodynic effect did not last greater than 24 h. Surprisingly, the non-selective COX inhibitor, piroxicam (60 microg) was without effect. These data agree with previous studies suggesting that spinal prostaglandin synthesis is important in the maintenance of hypersensitivity states following nerve injury. They differ from results in other models by suggesting that both COX isoenzymes are important in this spinal process, and for the first time demonstrate a remarkably long duration of action from a single intrathecal injection of ketorolac. Inhibition of spinal COX may be an important mechanism of action in treating some patients with neuropathic pain following peripheral nerve injury.

L5 ANSWER 10 OF 42 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002172952 EMBASE
TITLE: Corneal stimulation of MMP-1, -9 and uPA by platelet-activating factor is mediated by cyclooxygenase-2

metabolites.
AUTHOR: Ottino P.; Bazan H.E.P.
CORPORATE SOURCE: Dr. H.E.P. Bazan, LSU Eye Center, 2020 Gravier St., New Orleans, LA 70112, United States. hbazan1@lsuhsc.edu
SOURCE: Current Eye Research, (2002) 23/2 (77-85).
Refs: 43
ISSN: 0271-3683 CODEN: CEYRDM
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Purpose. This study was undertaken to evaluate the significance of cyclooxygenase-2 (COX-2) activity on urokinase plasminogen activator (uPA) and matrix metalloproteinases (MMPs)-1 and -9 induction in cornea following platelet-activating factor (PAF) treatment. Methods. Corneal organ cultures were pre-treated with increasing concentrations of COX-2-specific inhibitors **NS398** or nimesulide prior to PAF stimulation. To determine the effect of exogenous prostaglandins (PGs) on uPA, MMP-1 and MMP-9 levels, corneas were pre-treated with COX-2 inhibitors followed by the addition of 2.5 .mu.M PGD(2), PGE(2) or PGF(2.alpha.). The levels of uPA and MMP-9 were assayed by casein and gelatin zymography, respectively. MMP-1 levels were determined by Western Blot analysis. Results. The increase in uPA, MMP-9 and MMP-1 levels detected in corneal organ cultures treated with 100 nM cPAF was blocked by 5 .mu.M **NS398** and 10 .mu.M nimesulide, concentrations at which these inhibitors selectively inhibit COX-2 activity. Furthermore, pre-incubation with COX-2 inhibitors, followed by supplementation with PGD(2), PGE(2) or PGF(2.alpha.), increases uPA, MMP-9 and MMP-1 levels in corneas similar to and in some cases greater than that produced by cPAF **treatment** alone. Conclusions. During corneal **injury** and inflamation, PAF is an important factor in the activation of proteolytic cascades, which could lead to corneal epithelial defects and ultimately ulceration. One important goal in treating these defects is to modulate the activity of enzymes that destroy the extracellular matrix. Our results suggest that COX-2 induction following PAF stimulation and subsequent eicosanoid release may play a crucial role in the induction of uPA, MMP-1 and MMP-9 enzymes. Specific COX-2 inhibition could therefore block the actions of PAF when inflammation is sustained.

L5 ANSWER 11 OF 42 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2002374646 MEDLINE
DOCUMENT NUMBER: 22116128 PubMed ID: 12120008
TITLE: Effects of Celebrex and Zyflo on BOP-induced pancreatic cancer in Syrian hamsters.
AUTHOR: Wenger F A; Kilian M; Achucarro P; Heinicken D; Schimke I; Guski H; Jacobi C A; Muller J M
CORPORATE SOURCE: Clinic of General, Visceral, Vascular and Thoracic Surgery, Charite Campus Mitte, Schumannstrasse 20/21, D-10117 Berlin, Germany.. charipanc@aol.com
SOURCE: Pancreatology, (2002) 2 (1) 54-60.
Journal code: 100966936. ISSN: 1424-3903.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020718

Last Updated on STN: 20020808
Entered Medline: 20020807

AB BACKGROUND/AIMS: Selective inhibition of eicosanoid synthesis decreases inflammation, however, it is still unknown whether oxidative stress and carcinogenesis might be influenced in ductal pancreatic ductal cancer as well. METHODS: 120 male hamsters were randomized into 8 groups (n = 15). While control group 1-4 received 0.5 ml normal saline s.c. weekly for 16 weeks, groups 5-8 were injected 10 mg BOP/kg body weight to induce pancreatic cancer. After establishment of pancreatic cancer, groups 1 and 5 received no therapy, groups 2 and 6 were fed 7 mg Celebrex daily, groups 3 and 7 were given 28 mg Zyflo and groups 4 and 8 received Celebrex and Zyflo orally daily in weeks 17-32. In week 33, all animals were sacrificed, macroscopic size of pancreatic carcinomas was measured, incidence of pancreatic cancer was analyzed histopathologically and activities of antioxidative enzymes and concentration of products of lipid peroxidation in tumor-free and pancreatic intratumoral tissue were determined. RESULTS: Incidence and size of macroscopic **pancreatic** carcinomas were decreased by single **therapy** with Zyflo as well as combined therapy (Zyflo + Celebrex). Activities of antioxidative enzymes were increased and the concentration of products of lipid peroxidation was decreased in tumor-free pancreas. On the other hand, lipid peroxidation was increased in pancreatic tumors. CONCLUSION: Zyflo alone or in combination with Celebrex reduce tumor growth in pancreatic cancer and thus might be a new **therapeutic** option in advanced **pancreatic** cancer.

L5 ANSWER 12 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:394402 BIOSIS
DOCUMENT NUMBER: PREV200200394402
TITLE: Vioxx versus Toradol for acute postoperative pain.
AUTHOR(S): Urban, M. K. (1); Morelli, C. (1); Kelsey, W. T. (1)
CORPORATE SOURCE: (1) Hospital for Special Surgery, New York, NY USA
SOURCE: Anesthesia & Analgesia, (February, 2002) Vol. 94, No. 2S Supplement, pp. S.231. http://www.anesthesia-analgesia.org. print.
Meeting Info.: International Anesthesia Research Society 76th Clinical and Scientific Congress San Diego, CA, USA March 16-20, 2002
ISSN: 0003-2999.
DOCUMENT TYPE: Conference
LANGUAGE: English

L5 ANSWER 13 OF 42 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-083166 [11] WPIDS
DOC. NO. CPI: C2002-025278
TITLE: **Treating** or preventing ultraviolet **injury** to skin in mammalian subject comprises use of selective COX-2 inhibitor e.g. **celecoxib** or deracoxib, optionally with analgesic.
DERWENT CLASS: B03 B05
INVENTOR(S): SCHUH, J R; WILDER, K J
PATENT ASSIGNEE(S): (SCHU-I) SCHUH J R; (WILD-I) WILDER K J; (PHAA) PHARMACIA CORP
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001091856 A2		20011206	(200211)*	EN	19

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ

NL PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU
SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
US 2002009421 A1 20020124 (200214)
AU 2001075004 A 20011211 (200225)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001091856 A2		WO 2001-US17304	20010525
US 2002009421 A1	Provisional	US 2000-208798P	20000601
		US 2001-866196	20010525
AU 2001075004 A		AU 2001-75004	20010525

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001075004 A	Based on	WO 200191856

PRIORITY APPLN. INFO: US 2000-208798P 20000601; US 2001-866196 20010525
AN 2002-083166 [11] WPIDS
AB WO 200191856 A UPAB: 20020215
NOVELTY - **Treatment** of ultraviolet **injury** to skin in mammalian subject involves administering a selective COX-2 (cyclooxygenase-2) inhibitory drug (I) to the subject.
ACTIVITY - Antiinflammatory; Analgesic; Antipyretic; Vulnerary; Antiulcer; Antianemic; Hematostatic; Litholytic; Nephrotropic.
MECHANISM OF ACTION - COX-2 inhibitor.
USE - In the preparation of a medicament for **treating** or preventing ultraviolet **injury** to skin in a mammalian subject e.g. humans (claimed) and treat or relieve pain, fever and inflammation caused by the skin. The ultraviolet injury includes sunburn or skin hyperemia. Also useful for treating peptic ulcers, gastritis, regional enteritis, ulcerative colitis or diverticulitis, gastrointestinal lesions, gastrointestinal bleeding, coagulation disorders including anemia such as hypothrombinemia, hemophilia and other bleeding problems and kidney disease and for treating patients prior to surgery or patients taking anticoagulants. Also for treating edema, erythema, chillis, blistering and for preventing photodamage to the skin.
ADVANTAGE - The inhibitory drugs produce analgesic, antipyretic and anti-inflammatory responses. The drugs provide rapid relief of pain and other manifestations of acute UV injury to the skin.
Dwg.0/0

L5 ANSWER 14 OF 42 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-257665 [26] WPIDS
DOC. NO. CPI: C2001-077566
TITLE: Use of 5-HT1B/1D agonists in the treatment of otic pain, particularly that caused by caused by otitis media, otitis externa, otic surgery or swimmer's ear.
DERWENT CLASS: B02
INVENTOR(S): GAMACHE, D A; SHARIF, N A; YANNI, J M
PATENT ASSIGNEE(S): (ALCO-N) ALCON LAB INC
COUNTRY COUNT: 28
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001015677	A2	20010308	(200126)*	EN	22
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU BR CA CN JP MX PL TR US ZA					
AU 2000069174	A	20010326	(200137)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001015677	A2	WO 2000-US22764	20000818
AU 2000069174	A	AU 2000-69174	20000818

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000069174	A	Based on	WO 200115677

PRIORITY APPLN. INFO: US 1999-387358 19990831
AN 2001-257665 [26] WPIDS
AB WO 200115677 A UPAB: 20010515
NOVELTY - Composition for treating otic pain comprising one or more 1B/1D agonists, is new.

ACTIVITY - Analgesic; auditory.

No activity data given.

MECHANISM OF ACTION - 5-H1D (ID) and 5-HT1B (1B) agonists.

USE - The composition is for treating otic pain caused by otitis media, otitis externa, otic surgery or swimmer's ear (claimed). It can be used for acute treatment of temporary conditions, or may be administered chronically. The composition may also be used prophylactically, especially prior to otic surgery or noninvasive otic procedures or other types of surgery. It may also be used to **treat** pain due to allergens, inflammation, **trauma**, congestion, infection, foreign body sensation and surgery e.g. following cochlear implant surgery.

ADVANTAGE - The inhibition of pain is receptor specific, as opposed to non-specific such as local anesthetic treatment. This specific activity may reduce greatly reduce the number of dosings per day and also reduce the drawbacks of short duration of action and inhibition of wound healing which are associated with local anesthetics. Additionally serotonin receptor binding agents acting locally within otic tissue avoid the problems of tolerance, addiction and constipation associated with the chronic, systemic administration of opiates.

Dwg.0/0

L5 ANSWER 15 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6

ACCESSION NUMBER: 2001:248852 BIOSIS
DOCUMENT NUMBER: PREV200100248852
TITLE: Effects of specific inhibition of cyclo-oxygenase-1 and cyclo-oxygenase-2 in the rat stomach with normal mucosa and after acid challenge.
AUTHOR(S): Gretzer, Britta; Maricic, Nenad; Respondek, Michael; Schuligoi, Rufina; Peskar, Brigitta M. (1)
CORPORATE SOURCE: (1) Department of Experimental Clinical Medicine, Ruhr-University of Bochum, D-44780, Bochum: ekm@ruhr-uni-bochum.de Germany
SOURCE: British Journal of Pharmacology, (April, 2001) Vol. 132,

No. 7, pp. 1565-1573. print.
ISSN: 0007-1188.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB 1 Effects of the cyclo-oxygenase (COX)-1 inhibitor SC-560 and the COX-2 inhibitors rofecoxib and DFU were investigated in the normal stomach and after acid challenge. 2 In healthy rats, neither SC-560 nor rofecoxib (20 mg kg-1 each) given alone damaged the mucosa. Co-treatment with SC-560 and rofecoxib, however, induced severe lesions comparable to indomethacin (20 mg kg-1) whereas co-administration of SC-560 and DFU (20 mg kg-1 each) had no comparable ulcerogenic effect 5 h after dosing. 3 SC-560 (20 mg kg-1) inhibited gastric 6-keto-prostaglandin (PG) F1alpha by 86+-5% and platelet thromboxane (TX) B2 formation by 89+-4% comparable to indomethacin (20 mg kg-1). Rofecoxib (20 mg kg-1) did not inhibit gastric and platelet eicosanoids. 4 Intragastric HCl elevated mucosal mRNA levels of COX-2 but not COX-1. Dexamethasone (2 mg kg-1) prevented the up-regulation of COX-2. 5 After acid challenge, SC-560 (5 and 20 mg kg-1) induced dose-dependent injury. Rofecoxib (20 mg kg-1), DFU (5 mg kg-1) and dexamethasone (2 mg kg-1) given alone were not ulcerogenic but aggravated SC-560-induced damage. DFU augmented SC-560 damage 1 but not 5 h after administration whereas rofecoxib increased **injury** after both **treatment** periods suggesting different time courses. 6 Gastric injurious effects of rofecoxib and DFU correlated with inhibition of inflammatory PGE2. 7 The findings show that in the normal stomach lesions only develop when both COX-1 and COX-2 are inhibited. In contrast, during acid challenge inhibition of COX-1 renders the mucosa more vulnerable suggesting an important role of COX-1 in mucosal defence in the presence of a potentially noxious agent. In this function COX-1 is supported by COX-2. In the face of pending injury, however, COX-2 cannot maintain mucosal integrity when the activity of COX-1 is suppressed.

L5 ANSWER 16 OF 42 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001348654 EMBASE
TITLE: Pharmacologic **therapy** in traumatic brain **injury**: Update on experimental **treatment** strategies.
AUTHOR: Laurer H.L.; McIntosh T.K.
CORPORATE SOURCE: T.K. McIntosh, Department of Neurosurgery, Univ. of Pennsylvania Medical School, Veterans Administration Medical Ctr., 3320 Smith Walk, 105 Hayden Hall, Philadelphia, PA 19104-6316, United States. mcintosh@seas.upenn.edu
SOURCE: Current Pharmaceutical Design, (2001) 7/15 (1505-1516).
Refs: 132
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Considerable effort has led to an increased interest in emerging preclinical and clinical data regarding the pathophysiological changes in the posttraumatic brain. It is widely believed that delayed cell damage and death contributes to behavioral impairment following traumatic brain **injury**. However, no drug **therapy** to attenuate this process is available at present, and the development of new therapeutic regimen is urgently warranted. This manuscript represents a compendium of

recent preclinical work undertaken to evaluate new pharmacologic strategies in the experimental setting as a first step towards the development of a therapeutic armamentarium directed to improve functional recovery in head-injured patients.

L5 ANSWER 17 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:259802 BIOSIS
DOCUMENT NUMBER: PREV200100259802
TITLE: Impaired intestinal T cell function may cause enhanced gut bacterial translocation in burn injury.
AUTHOR(S): Choudhry, Mashkoor A. (1); Fazal, Nadeem (1); Namak, Shahla Y. (1); Haque, Farah (1); Ravindranath, Thyyar (1); Sayeed, Mohammed M. (1)
CORPORATE SOURCE: (1) Loyola University Chicago Medical School, 2160 South First Ave, Maywood, IL, 60153 USA
SOURCE: FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1123. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Increased gut bacterial translocation in burn and trauma patients has been demonstrated in a number of previous studies, however, the mechanism for such an increased gut bacterial translocation in injured patients remains poorly understood. Utilizing a rat model of burn injury, in the present study we examined the role of intestinal immune defense by analyzing the T cell functions. We investigated if intestinal T cells dysfunction contributes to bacterial translocation after burn injury. Also our study determined if burn-mediated alterations in intestinal T cell functions are related to enhanced release of PGE2. Finally, we examined whether or not burn-related alterations in intestinal T cell function are due to inappropriate activation of signaling molecule P59fyn which is required for T cell activation and proliferation. A significant increase in gut bacterial accumulation in MLN on day 3 after burn injury (11 +- 2.6, CFU) was observed compared to sham injury (0.8 +- 0.5). This was accompanied by a significant decrease in the proliferation of T cells of PP (65,232 +- 50,186, DPM) and MLN (173,023 +- 5,197) of burn rats compared to the T cells derived form PP (306,213 +- 20,491) and MLN (346,0245 +- 18,098) of sham animals. The **treatments** of **burn** animals with PGE2 synthesis blockers **NS398** or with indomethacin prevented the decrease in PP and MLN T cell proliferation as well as enhanced bacterial translocation. Finally, our data suggested that the inhibition of intestinal T cell proliferation could result via PGE2-mediated down-regulation of the T cell activation-signaling molecule P59fyn. These findings support a role of T cell mediated immune defense against gut bacterial translocation in burn injury.

L5 ANSWER 18 OF 42 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2001459072 MEDLINE
DOCUMENT NUMBER: 21396314 PubMed ID: 11504793
TITLE: Cell cycle effects of nonsteroidal anti-inflammatory drugs and enhanced growth inhibition in combination with gemcitabine in pancreatic carcinoma cells.
AUTHOR: Yip-Schneider M T; Sweeney C J; Jung S H; Crowell P L; Marshall M S
CORPORATE SOURCE: Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana 46202, USA..

mtipschn@iupui.edu
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2001 Sep) 298 (3) 976-85.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010816
Last Updated on STN: 20010917
Entered Medline: 20010913

AB Increased cyclooxygenase-2 (COX-2) expression in human pancreatic adenocarcinomas, as well as the growth-inhibitory effect of nonsteroidal anti-inflammatory drugs (NSAIDs) in vitro, suggests that NSAIDs may be an effective **treatment** for **pancreatic** cancer. Gemcitabine is currently the most effective chemotherapeutic drug available for patients with pancreatic cancer, but is only minimally effective against this aggressive disease. Clearly, other treatment options must be identified. To design successful therapeutic strategies involving compounds either alone or in combination with others, it is necessary to understand their mechanism of action. In the present study, we evaluated the effects of three NSAIDs (sulindac, indomethacin, and **NS-398**) or gemcitabine in two human pancreatic carcinoma cell lines, BxPC-3 (COX-2-positive) and PaCa-2 (COX-2-negative), previously shown to be growth-inhibited by these NSAIDs. Effects on cell cycle and apoptosis were investigated by flow cytometry or Western blotting. Treatment with NSAIDs or gemcitabine altered the cell cycle phase distribution as well as the expression of multiple cell cycle regulatory proteins in both cell lines, but did not induce substantial levels of apoptosis. Furthermore, we demonstrated that the combination of the NSAID sulindac or **NS-398** with gemcitabine inhibited cell growth to a greater degree than either compound alone. These results indicate that the antiproliferative effects of NSAIDs and gemcitabine in pancreatic tumor cells are primarily due to inhibition of cell cycle progression rather than direct induction of apoptotic cell death, regardless of COX-2 expression. In addition, NSAIDs in combination with gemcitabine may hold promise in the clinic for the **treatment** of **pancreatic** cancer.

L5 ANSWER 19 OF 42 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2002030571 MEDLINE
DOCUMENT NUMBER: 21595424 PubMed ID: 11734496
TITLE: A cyclooxygenase-2 inhibitor impairs ligament healing in the rat.
AUTHOR: Elder C L; Dahners L E; Weinhold P S
CORPORATE SOURCE: Department of Orthopaedic Surgery, University of North Carolina at Chapel Hill, 27599-7055, USA.
SOURCE: AMERICAN JOURNAL OF SPORTS MEDICINE, (2001 Nov-Dec) 29 (6) 801-5.
Journal code: 7609541. ISSN: 0363-5465.
PUB. COUNTRY: United States
DOCUMENT TYPE: (EVALUATION STUDIES)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020124
Last Updated on STN: 20020404
Entered Medline: 20020402

AB **Celecoxib** was the first of a new class of nonsteroidal antiinflammatory drugs, the cyclooxygenase-2 (COX-2) specific inhibitors, marketed as having the same antiinflammatory efficacy as other nonsteroidal antiinflammatory drugs without their increased risk of gastrointestinal ulceration. Among the widest uses of nonsteroidal antiinflammatory drugs is in the **treatment** of acute soft tissue **injuries**. Although the benefits of **celecoxib** have been shown when used for rheumatoid arthritis and osteoarthritis, we are unaware of any studies concerning its effect on soft tissues. We used the surgically incised medial collateral ligament of male Sprague-Dawley rats as an experimental model for acute ligament injuries to investigate the effects of **celecoxib** on ligament healing. Fifty rats underwent surgical transection of the right medial collateral ligament. Postoperatively, half were given **celecoxib** for the first 6 days of recovery, the other half were not. The animals were sacrificed 14 days after the operation, and both the injured and uninjured medial collateral ligaments were mechanically tested to failure in tension. **Celecoxib-treated/injured** ligaments were found to have a 32% lower load to failure than untreated/injured ligaments. The results of this study do not support use of cyclooxygenase-2 specific inhibitors in the **treatment** of ligament **injuries**.

L5 ANSWER 20 OF 42 MEDLINE
ACCESSION NUMBER: 2001475403 MEDLINE
DOCUMENT NUMBER: 21410007 PubMed ID: 11518732
TITLE: Inhibition of cyclooxygenase-2 aggravates doxorubicin-mediated cardiac injury in vivo.
AUTHOR: Dowd N P; Scully M; Adderley S R; Cunningham A J; Fitzgerald D J
CORPORATE SOURCE: Department of Anaesthesia and Intensive Care, Beaumont Hospital, Dublin, Ireland.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (2001 Aug) 108 (4) 585-90.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010827
Last Updated on STN: 20010924
Entered Medline: 20010920

AB The clinical use of doxorubicin, an anthracycline chemotherapeutic agent, is limited by cardiotoxicity, particularly when combined with herceptin, an antibody that blocks the HER2 receptor. Doxorubicin induces cyclooxygenase-2 (COX-2) activity in rat neonatal cardiomyocytes. This expression of COX-2 limits doxorubicin-induced cardiac cell injury, raising the possibility that the administration of a prostaglandin may protect the heart during the in vivo administration of doxorubicin. Doxorubicin (15 mg/kg) administered to adult male Sprague Dawley rats induced COX-2 expression and activity in cardiac tissue. Prostacyclin generation measured as the excretion of 2,3-dinor-6-keto-PGF(1alpha) also increased, and this was blocked by a COX-2 inhibitor, SC236. In contrast, administration of a COX-1 inhibitor SC560 at a dose that reduced serum thromboxane B2 by more than 80% did not prevent the doxorubicin-induced increase in prostacyclin generation. Doxorubicin increased cardiac injury, detected as a rise in plasma cardiac troponin T, serum lactate dehydrogenase, and cardiomyocyte apoptosis; this was aggravated by coadministration of SC236 but not SC560. The degree of **injury** in animals **treated** with a combination of doxorubicin and SC236 was

attenuated by prior administration of the prostacyclin analogue iloprost. These data raise the possibility of protecting the heart during the administration of doxorubicin by prior administration of prostacyclin.

L5 ANSWER 21 OF 42 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 2001505297 MEDLINE
DOCUMENT NUMBER: 21234576 PubMed ID: 11336442
TITLE: Reduction of pathological and behavioral deficits following spinal cord contusion injury with the selective cyclooxygenase-2 inhibitor **NS-398**.
AUTHOR: Hains B C; Yucra J A; Hulsebosch C E
CORPORATE SOURCE: Department of Anatomy and Neurosciences and Marine Biomedical Institute, University of Texas Medical Branch, Galveston 77555-1069, USA.
CONTRACT NUMBER: NS11255 (NINDS)
NS39161 (NINDS)
SOURCE: JOURNAL OF NEUROTRAUMA, (2001 Apr) 18 (4) 409-23.
Journal code: 8811626. ISSN: 0897-7151.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010917
Last Updated on STN: 20010917
Entered Medline: 20010913

AB Spinal cord injury (SCI) results in loss of locomotor function and development of abnormal chronic pain syndromes (mechanical allodynia, thermal hyperalgesia). Following injury, secondary mechanisms including release of excitatory amino acids, inflammation and lipid peroxidation damage neural cells through release of cytotoxic free radicals. We hypothesized that selective inhibition of cyclooxygenase-2 (COX-2), an inducible inflammatory mediator, would decrease tissue damage and subsequently reduce locomotor deficits and development of chronic central pain syndromes after injury. Fifteen minutes prior to receiving T13 spinal segment spinal cord contusion injury, 200-225-g male Sprague-Dawley rats received either vehicle (0.5 ml 1:1 v/v DMSO/saline, i.p., n = 20) or the selective COX-2 inhibitor **NS-398** (5 mg/kg in DMSO/saline v/v, i.p., n = 20). Locomotor function via the BBB scale, and nociceptive behaviors measured by paw withdrawals to von Frey filaments and radiant heat stimuli were tested for 4 weeks postinjury. Histological examination and volumetric analysis of spinal cord tissue were performed concomitantly. Spinally contused animals receiving **NS-398** demonstrated significantly ($p < 0.05$) reduced locomotor alteration and reductions in both fore- and hindlimb mechanical allodynia and thermal hyperalgesia when compared to vehicle controls. Histological examination of spinal segments at the lesion segment demonstrated reduced lesion extent and increased viable tissue when compared to vehicle controls. Prostaglandin E2 levels were significantly lowered in **NS-398**-treated but not vehicle-**treated** animals 12 h after **injury**. These results support the role of COX-2 in reducing pathological and behavioral deficits after spinal cord injury.

L5 ANSWER 22 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:479050 BIOSIS
DOCUMENT NUMBER: PREV200100479050
TITLE: Efficacy of **celecoxib** vs naproxen in the treatment of ankle sprain.
AUTHOR(S): Petrella, R. (1); Ekman, E. (1); Levy, S. (1); Johnson, T. (1); Fort, J. (1)

CORPORATE SOURCE: (1) Center for Activity and Ageing, University of Western Ontario, London, ON Canada
SOURCE: Medicine & Science in Sports & Exercise, (May, 2001) Vol. 33, No. 5 Supplement, pp. S200. print.
Meeting Info.: 48th Annual Meeting of the American College of Sports Medicine Baltimore, Maryland, USA May 30-June 02, 2001
ISSN: 0195-9131.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L5 ANSWER 23 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:479047 BIOSIS
DOCUMENT NUMBER: PREV200100479047
TITLE: Efficacy of **celecoxib** vs ibuprofen in the treatment of ankle sprain.
AUTHOR(S): Ekman, E. (1); Petrella, R. (1); Levy, S. (1); McDonald, S. (1); Fort, J. (1)
CORPORATE SOURCE: (1) Southern Orthopaedic Sports Medicine, Columbia, SC USA
SOURCE: Medicine & Science in Sports & Exercise, (May, 2001) Vol. 33, No. 5 Supplement, pp. S198. print.
Meeting Info.: 48th Annual Meeting of the American College of Sports Medicine Baltimore, Maryland, USA May 30-June 02, 2001
ISSN: 0195-9131.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L5 ANSWER 24 OF 42 MEDLINE
ACCESSION NUMBER: 2001488604 MEDLINE
DOCUMENT NUMBER: 21421861 PubMed ID: 11531019
TITLE: PGE2 suppresses intestinal T cell function in thermal injury: a cause of enhanced bacterial translocation.
AUTHOR: Choudhry M A; Fazal N; Namak S Y; Haque F; Ravindranath T; Sayeed M M
CORPORATE SOURCE: Burn and Shock Trauma Institute, Department of Surgery and Physiology, Loyola University Chicago Medical Center Maywood, Illinois 60153, USA.
CONTRACT NUMBER: GM53235 (NIGMS)
GM56865 (NIGMS)
SOURCE: SHOCK, (2001 Sep) 16 (3) 183-8.
Journal code: 9421564. ISSN: 1073-2322.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20010904
Last Updated on STN: 20020319
Entered Medline: 20020318

AB Increased gut bacterial translocation in burn and trauma patients has been demonstrated in a number of previous studies, however, the mechanism for such an increased gut bacterial translocation in injured patients remains poorly understood. Utilizing a rat model of burn injury, in the present study we examined the role of intestinal immune defense by analyzing the T cell functions. We investigated if intestinal T cells dysfunction contributes to bacterial translocation after burn injury. Also our study determined if burn-mediated alterations in intestinal T cell functions are

related to enhanced release of PGE2. Finally, we examined whether or not burn-related alterations in intestinal T cell function are due to inappropriate activation of signaling molecule P59fyn, which is required for T cell activation and proliferation. The results presented here showed an increase in gut bacterial accumulation in mesenteric lymph nodes after thermal injury. This was accompanied by a decrease in the intestinal T cell proliferative responses. Furthermore, the **treatments** of **burn-injured** animals with PGE2 synthesis blocker (indomethacin or **NS398**) prevented both the decrease in intestinal T cell proliferation and enhanced bacterial translocation. Finally, our data suggested that the inhibition of intestinal T cell proliferation could result via PGE2-mediated down-regulation of the T cell activation-signaling molecule P59fyn. These findings support a role of T cell-mediated immune defense against bacterial translocation in burn injury.

L5 ANSWER 25 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:487332 BIOSIS
DOCUMENT NUMBER: PREV200100487332
TITLE: Burn injury enhances brain prostaglandin E2 production through induction of cyclooxygenase-2 and prostaglandin E2 synthase in vascular endothelial cells in rats.
AUTHOR(S): Ozaki, Y. (1); Matsumura, K.; Ibuki, T. (1); Yamazaki, Y. (1); Ueda, M. (1); Lijima, N.; Tanaka, Y. (1); Kobayashi, S.
CORPORATE SOURCE: (1) Dept. of Anesthesiol., Kyoto Prefectural Univ. of Med., Kyoto Japan
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 144. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Burn injury often evokes acute phase response, which is partly mediated by the central nervous system (CNS). In this study, we examined in rats whether burn injury induces prostaglandin E2 (PGE2), the central mediator of acute phase response, and enzymes for PGE2 production in the CNS. Male SD rats received either approximately 50% full-thickness **burn injury** or sham-**treatment**. At 36 hours after the **injury**, the cerebrospinal fluid (CSF) was sampled for the measurement of PGE2, and the brain and the spinal cord were sampled for the immunohistochemical detection of cyclooxygenase-2 (COX-2) and microsomal-type PGE synthase (mPGES). PGE2 level in the CSF was significantly elevated in the injured rats, and this elevation was suppressed by a COX-2-specific inhibitor, **NS398**. Only in the injured rats, COX-2 and mPGES proteins were detected in vascular endothelial cells throughout the CNS with no regional difference. Double-immunofluorescent study revealed COX-2 and mPGES are colocalized in the perinuclear region of the endothelial cells. These results indicate that burn injury elevates brain PGE2 level through the induction of COX-2 and mPGES in endothelial cells of the CNS.

L5 ANSWER 26 OF 42 MEDLINE
ACCESSION NUMBER: 2002120388 MEDLINE
DOCUMENT NUMBER: 21828729 PubMed ID: 11840344
TITLE: Corneal stimulation of MMP-1, -9 and uPA by platelet-activating factor is mediated by cyclooxygenase-2

metabolites.
AUTHOR: Ottino P; Bazan H E
CORPORATE SOURCE: Department of Ophthalmology and Neuroscience Center, LSU Health Sciences Center, New Orleans, Louisiana 70112, USA.
CONTRACT NUMBER: EY04928 (NEI)
SOURCE: CURRENT EYE RESEARCH, (2001 Aug) 23 (2) 77-85.
Journal code: 8104312. ISSN: 0271-3683.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020222
Last Updated on STN: 20020312
Entered Medline: 20020311

AB PURPOSE: This study was undertaken to evaluate the significance of cyclooxygenase-2 (COX-2) activity on urokinase plasminogen activator (uPA) and matrix metalloproteinases (MMPs)-1 and -9 induction in cornea following platelet-activating factor (PAF) treatment. METHODS: Corneal organ cultures were pre-treated with increasing concentrations of COX-2-specific inhibitors **NS398** or nimesulide prior to PAF stimulation. To determine the effect of exogenous prostaglandins (PGs) on uPA, MMP-1 and MMP-9 levels, corneas were pre-treated with COX-2 inhibitors followed by the addition of 2.5 microM PGD2, PGE2 or PGF2alpha. The levels of uPA and MMP-9 were assayed by casein and gelatin zymography, respectively. MMP-1 levels were determined by Western Blot analysis. RESULTS: The increase in uPA, MMP-9 and MMP-1 levels detected in corneal organ cultures treated with 100 nM cPAF was blocked by 5 microM **NS398** and 10 microM nimesulide, concentrations at which these inhibitors selectively inhibit COX-2 activity. Furthermore, pre-incubation with COX-2 inhibitors, followed by supplementation with PGD2, PGE2 or PGF 2alpha, increases uPA, MMP-9 and MMP-1 levels in corneas similar to and in some cases greater than that produced by cPAF **treatment** alone. CONCLUSIONS: During corneal **injury** and inflamation, PAF is an important factor in the activation of proteolytic cascades, which could lead to corneal epithelial defects and ultimately ulceration. One important goal in treating these defects is to modulate the activity of enzymes that destroy the extracellular matrix. Our results suggest that COX-2 induction following PAF stimulation and subsequent eicosanoid release may play a crucial role in the induction of uPA, MMP-1 and MMP-9 enzymes. Specific COX-2 inhibition could therefore block the actions of PAF when inflammation is sustained.

L5 ANSWER 27 OF 42 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 2001277260 MEDLINE
DOCUMENT NUMBER: 21262279 PubMed ID: 11368536
TITLE: **NS-398 treatment** after **trauma** modifies NF-kappaB activation and improves survival.
AUTHOR: Mack Strong V E; Mackrell P J; Concannon E M; Mestre J R; Smyth G P; Schaefer P A; Stapleton P P; Daly J M
CORPORATE SOURCE: Department of Surgery, New York Presbyterian Hospital-Weill Medical College of Cornell University, New York, New York 10021, USA.. vem9002@nyp.org
SOURCE: JOURNAL OF SURGICAL RESEARCH, (2001 Jun 1) 98 (1) 40-6.
Journal code: 0376340. ISSN: 0022-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010702
Last Updated on STN: 20010702
Entered Medline: 20010628

AB Prostaglandin E(2) (PGE(2)) production after trauma contributes to immune alterations that increase susceptibility to infections. We hypothesize that blocking PGE(2) with **NS-398**, a selective COX-2 inhibitor, will modulate this response and improve outcome. This study evaluated the effect of **NS-398** given over 7 days on proinflammatory cytokines, intracellular signaling, and survival after a septic challenge. Balb/C mice (n = 8/group) were given 10 mg/kg **NS -398** intraperitoneally over 7 days, starting after anesthesia or trauma (femur fracture + 40% hemorrhage). Four groups, anesthesia + vehicle (C), anesthesia + **NS-398** (CN), trauma + vehicle (T), or trauma + **NS-398** (TN), were studied. On Day 7 after trauma, mice were sacrificed, serum was collected, and splenic macrophages were evaluated for PGE(2), LTB(4), IL-6, TNF-alpha, and NO production. Additionally, macrophage COX-2 mRNA, IkappaB-alpha, and NF-kappaB were evaluated. In a separate study, mice (n = 10-11/group) were traumatized and given **NS-398** over 7 days, and then cecal ligation and puncture (CLP) were performed. Mice were then followed for survival over 10 days (via log-rank test). **NS-398** **treatment** of **injured** mice decreased PGE(2) production compared to T (3.9 +/- 0.3 vs 3.1 +/- 0.4 pg/microg protein), and significantly decreased IL-6, NO, and TNF-alpha production. **NS-398** treatment also attenuated COX-2 mRNA levels and NF-kappaB activation. These cellular events correlate with a significant survival advantage in TN versus T mice after CLP. These data suggest that a specific COX-2 inhibitor not only suppresses PGE(2), but normalizes proinflammatory cytokines after trauma through changes that may partly be mediated via transcriptional events. This correlates with significantly increased survival in TN mice given a septic challenge and suggests that COX-2 inhibitors contribute to modulating the inflammatory response and improving survival after trauma.

L5 ANSWER 28 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:211176 BIOSIS
DOCUMENT NUMBER: PREV200200211176
TITLE: Inhibition of cyclooxygenase-2 (COX-2) enzyme ameliorates the severity of caerulein-induced pancreatitis and associated lung injury in mice.
AUTHOR(S): Song, Albert M. (1); Bhagat, Lakshmi (1); Singh, Vijay P. (1); Mykoniatis, Andreas (1); van Acker, Gijs J. D. (1); Saluja, Ashok K. (1); Steer, Michael L. (1)
CORPORATE SOURCE: (1) Beth Israel Deaconess Medical Ctr, Harvard Medical Sch, Boston, MA USA
SOURCE: Gastroenterology, (April, 2001) Vol. 120, No. 5 Supplement 1, pp. A.537. http://www.gastrojournal.org/. print.
Meeting Info.: 102nd Annual Meeting of the American Gastroenterological Association and Digestive Disease Week Atlanta, Georgia, USA May 20-23, 2001
ISSN: 0016-5085.
DOCUMENT TYPE: Conference
LANGUAGE: English

L5 ANSWER 29 OF 42 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-061450 [07] WPIDS
DOC. NO. CPI: C2001-017020
TITLE: Topical formulations, used for transdermal delivery of

agents e.g. (anti)hormones, comprise diol penetration enhancer e.g. 1,2-propanediol and cell envelope-disrupting agent e.g. oleic acid.

DERWENT CLASS: B05 B07
INVENTOR(S): RAGAVAN, V V
PATENT ASSIGNEE(S): (AVIA-N) AVIANA BIOPHARM
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000072883	A2	20001207	(200107)*	EN	25

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2000054608 A 20001218 (200118)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000072883	A2	WO 2000-US15289	20000602
AU 2000054608	A	AU 2000-54608	20000602

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000054608	A	Based on	WO 200072883

PRIORITY APPLN. INFO: US 1999-137186P 19990602
AN 2001-061450 [07] WPIDS
AB WO 200072883 A UPAB: 20011129
NOVELTY - Topical formulations comprising a penetration enhancer consisting essentially of a diol and a cell envelope-disrupting agent.
USE - The topical formulations are used for the transdermal delivery of active agents through compromised skin, including hormones, antihormones, corticosteroids, antiviral agents, phosphodiesterase enzyme inhibitors, ICAM-1 inhibitors, substances that affect the formation and aggregation of melanin granules, inhibitors of enzymes that participate in the cascade of reactions responsible for cell death, and non-steroidal antiinflammatory drugs, particularly caspasine, estrogens, progestogens, androgens, estrogen metabolites, progestogens, androgens, antiandrogens, **celecoxib**, rofecoxib, danazole, acyclovir, ibuprofen, diclofenac, naproxen, piroxicam, phenybutazone, etfenamate, sulindac, salicylic acid, indomethacin, spironolactone, cyproterone acetate, finasteride, flutamide, Casodex (RTM: bicalutamide) and other substances known to inhibit post-receptor events and transformation of testosterone to active androgens (claimed). They are used to **treat** skin disorders such as **burns** (minor and major burns, sunburn), cuts, insect bites, psoriasis, burns with loss of the epidermis and/or part of the dermis such as in skin resurfacing procedures through chemical, laser and other agents, disorders due to the action of toxic agents such as poison ivy, radiation therapy, chemotherapy or other chemical and non-chemical skin-disrupting agents, local tissue conditions such as local muscle injury, inflammation, arthritis or infection, and to treat compromised skin (claimed). They may also be used to treat pemphigus and hirsutism,

acne, osteoarthritis, local muscle injury due to sports or falls, local bacterial and viral infections, angina and hypogonadism due to testosterone deficiency and to provide hormone replacement therapy and contraception. In the absence of enhancer, the compositions can be used to treat compromised skin.

ADVANTAGE - The compositions allow delivery of substances to the organs of the skin, such as the hair follicles and sebaceous glands, to the tissues under the skin, such as the muscles, joints and related tissues, and to the systemic circulation.

DESCRIPTION OF DRAWING(S) - Graph of the transdermal penetration over time of flutamide alone and in combination with a formulation containing oleic acid as enhancer.

Dwg.1/2

L5 ANSWER 30 OF 42 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2000-126678 [11] WPIDS
CROSS REFERENCE: 1999-214603 [18]; 2002-225937 [28]
DOC. NO. NON-CPI: N2000-095473
DOC. NO. CPI: C2000-038602
TITLE: Pain relieving compositions suitable for transdermal administration comprise biphasically soluble amines.
DERWENT CLASS: B02 B05 B07 D22 P32
INVENTOR(S): MURDOCK, R W; WILLIAMS, C D
PATENT ASSIGNEE(S): (PRAE-N) PRAECIS PHARM INC; (PHAR-N) PHARM APPL ASSOC LLC; (PHAR-N) PHARM APPL ASOCIATES LLC; (MURD-I) MURDOCK R W; (WILL-I) WILLIAMS C D
COUNTRY COUNT: 87
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000000120	A1	20000106	(200011)*	EN	70
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
AU 9948415	A	20000117	(200026)		
NO 2000006604	A	20010228	(200121)		
EP 1093348	A1	20010425	(200124)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
BR 9912508	A	20010502	(200129)		
CZ 2000004823	A3	20010613	(200138)		
SK 2000002001	A3	20010806	(200157)		
US 2001029257	A1	20011011	(200162)		
US 6290986	B1	20010918	(200173)		18
KR 2001078754	A	20010821	(200212)		
ZA 2001000443	A	20011224	(200212)		75
CN 1331576	A	20020116	(200230)		
HU 2001002728	A2	20020328	(200234)		
JP 2002519310	W	20020702	(200246)		81

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000000120	A1	WO 1999-US14653	19990629
AU 9948415	A	AU 1999-48415	19990629
NO 2000006604	A	WO 1999-US14653	19990629

			NO 2000-6604	20001222
EP 1093348	A1		EP 1999-932017	19990629
			WO 1999-US14653	19990629
BR 9912508	A		BR 1999-12508	19990629
			WO 1999-US14653	19990629
CZ 2000004823	A3		WO 1999-US14653	19990629
			CZ 2000-4823	19990629
SK 2000002001	A3		WO 1999-US14653	19990629
			SK 2000-2001	19990629
US 2001029257	A1	Provisional	US 1996-29120P	19961024
		CIP of	US 1997-957485	19971024
		CIP of	US 1998-106684	19980629
		Provisional	US 1999-122903P	19990305
		CIP of	US 1999-342679	19990629
			US 2001-754500	20010103
US 6290986	B1	Provisional	US 1996-29120P	19961024
		CIP of	US 1997-957485	19971024
		CIP of	WO 1997-US19651	19971024
			US 1998-106684	19980629
KR 2001078754	A		KR 2000-714985	20001229
ZA 2001000443	A		ZA 2001-443	20010116
CN 1331576	A		CN 1999-810055	19990629
HU 2001002728	A2		WO 1999-US14653	19990629
			HU 2001-2728	19990629
JP 2002519310	W		WO 1999-US14653	19990629
			JP 2000-556706	19990629

FILING DETAILS:

PATENT NO	KIND		PATENT NO	
AU 9948415	A	Based on	WO 200000120	
EP 1093348	A1	Based on	WO 200000120	
BR 9912508	A	Based on	WO 200000120	
CZ 2000004823	A3	Based on	WO 200000120	
SK 2000002001	A3	Based on	WO 200000120	
US 2001029257	A1		20 011110 WO	9911208
HU 2001002728	A2	Based on	WO 200000120	
JP 2002519310	W	Based on	WO 200000120	

PRIORITY APPLN. INFO: US 1999-122903P 19990305; US 1998-106684 19980629; WO 1997-US19651 19971024

AN 2000-126678 [11] WPIDS

CR 1999-214603 [18]; 2002-225937 [28]

AB WO 200000120 A UPAB: 20020722

NOVELTY - Pain relieving compositions suitable for transdermal administration comprise biphasically soluble amines.

DETAILED DESCRIPTION - Transdermal compositions for treating pain comprise:

(A) therapeutic amounts of amine-containing compound (I) with biphasic solubility;

(B) a pharmaceutical carrier for transdermal delivery; and optionally

(C) compounds that enhance the therapeutic activity of (I).

INDEPENDENT CLAIMS are included for:

(1) transdermal compositions for treating pain comprising therapeutic amounts of an afferent (sensory) neuron transmission blocker with biphasic solubility and a pharmaceutical carrier for transdermal delivery; and

(2) a method for selecting compounds suitable for treating pain comprising: (a) transdermally administering (I); and (b) measuring pain relief to determine efficacy.

ACTIVITY - Analgesic; muscle relaxant; sensory nerve blocker; antidepressant; antiinflammatory; antiepileptic; anticonvulsant; hypotensive; vasotropic.

MECHANISM OF ACTION - Sodium channel blocker; adrenergic agonist.

USE - Useful in the **treatment** of pain associated with **trauma** Herpes zoster, chemical injury and late stage cancer. Also useful for the assessment of transdermal pain relieving compositions.

ADVANTAGE - Unwanted side effects of oral administration (e.g. gastrointestinal and hepatotoxicity) and the inconvenience of injections are avoided.

Dwg.0/2

L5 ANSWER 31 OF 42 MEDLINE DUPLICATE 11

ACCESSION NUMBER: 2000416717 MEDLINE
DOCUMENT NUMBER: 20409455 PubMed ID: 10953335
TITLE: Blockade of cyclooxygenase-2 inhibits proliferation and induces apoptosis in human pancreatic cancer cells.
AUTHOR: Ding X Z; Tong W G; Adrian T E
CORPORATE SOURCE: Department of Biomedical Sciences, Creighton University School of Medicine, Omaha, NE 68178, USA.
CONTRACT NUMBER: P50CA72712 (NCI)
SOURCE: ANTICANCER RESEARCH, (2000 Jul-Aug) 20 (4) 2625-31. Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000907
Last Updated on STN: 20000907
Entered Medline: 20000831

AB Cyclooxygenase (COX), also referred to as prostaglandin endoperoxide synthase, is a key enzyme in the conversion of arachidonic acid to prostaglandins and other eicosanoids. Epidemiologic, animal and in vitro observations show a positive correlation between the expression of COX (especially COX-2) and colonic cancer development, growth and apoptosis. Constitutive expression of COX-2 in human pancreatic cancer cells was recently reported. To evaluate the potential role of COX in pancreatic cancer, RT-PCR was used to determine the constitutive expression of COX-2 in four pancreatic cancer cell lines. MiaPaCa2, PANC-1, HPAF, ASPC-1. The effect of COX blockade with either the general COX inhibitor, indomethacin, or the specific COX-2 inhibitor, **NS-398**, on [3H]-thymidine incorporation and cell number was investigated in these four pancreatic cancer cell lines. In addition, the effects of these COX inhibitors on pancreatic cancer cell apoptosis was evaluated by DNA propidium iodide staining and the terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL) assay. All four human pancreatic cancer cell lines expressed COX-2 and their proliferation was concentration- and time-dependently inhibited by both indomethacin andNS398. Substantial apoptosis was also induced by **treatment** of **pancreatic** cancer cells with either indomethacin or **NS398**, as indicated by both DNA propidium iodide staining and the TUNEL assay. Furthermore, indomethacin and **NS398** were equipotent for growth inhibition and induction of apoptosis, indicating that eicosanoid synthesis via COX-2 is involved in pancreatic cancer cell proliferation and survival. In conclusion, these findings suggest that the COX pathway, especially COX-2, contributes to the growth and apoptosis of pancreatic cancer. Specific COX-2 inhibitors are likely to be valuable for the treatment and prevention of this deadly cancer.

L5 ANSWER 32 OF 42 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 2001053993 MEDLINE
DOCUMENT NUMBER: 20370379 PubMed ID: 10914695
TITLE: COX-2 specific inhibitors offer improved advantages over traditional NSAIDs.
AUTHOR: Urban M K
CORPORATE SOURCE: Hospital for Special Surgery, New York, NY 10021, USA.
SOURCE: ORTHOPEDICS, (2000 Jul) 23 (7 Suppl) S761-4. Ref: 12
Journal code: 7806107. ISSN: 0147-7447.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001212

AB Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed medications worldwide and are often the first choice of **treatment** for acute myalgias, orthopedic **injuries**, postoperative pain, chronic rheumatoid arthritis, and osteoarthritis. The mechanism through which NSAIDs provide analgesia and suppress inflammation is the inhibition of the enzyme cyclooxygenase, resulting in decreased prostaglandin synthesis. The suppression of prostaglandin synthesis can also produce gastric and renal toxicity, as well as impair normal platelet function. Thus, NSAIDs are associated with potentially harmful side effects. Cyclooxygenase exists in two isoenzymatic forms, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Cyclooxygenase-1 appears to be constitutively expressed in many tissues and produces prostaglandins, which regulate normal cellular functions. However, COX-2 activity is induced by proinflammatory cytokines and produces prostaglandins that mediate the inflammatory response and pain signaling transmission. Traditional nonspecific NSAIDs inhibit both COX-1 and COX-2, and in doing so, not only decrease inflammation and pain, but also promote gastrointestinal tract damage and bleeding. The potential clinical benefit of COX-2 inhibitors is significant due to the number of patients chronically treated with NSAIDs and the three- to ten-fold higher risk of gastrointestinal injury and death associated with traditional NSAIDs. Recently, a class of anti-inflammatory medications has been developed that primarily inhibits COX-2 while sparing the enzymatic activity of COX-1 at therapeutic dosages. Two medications that predominantly inhibit only COX-2, rofecoxib and **celecoxib**, are currently available by prescription in the United States.

L5 ANSWER 33 OF 42 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 2000164197 MEDLINE
DOCUMENT NUMBER: 20164197 PubMed ID: 10683192
TITLE: Wound collagen deposition in rats: effects of an NO-NSAID and a selective COX-2 inhibitor.
AUTHOR: Muscara M N; McKnight W; Asfaha S; Wallace J L
CORPORATE SOURCE: Department of Pharmacology, University of Calgary, 3330 Hospital Drive NW, Calgary, AB, T2N 4N1, Canada.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (2000 Feb) 129 (4) 681-6.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000810
Last Updated on STN: 20000810
Entered Medline: 20000727

AB Selective cyclo-oxygenase (COX)-2 inhibitors and nitric oxide-releasing nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit reduced toxicity in the gastrointestinal tract, but may affect wound healing in other tissues. In this study, we have compared the effects of a selective COX-2 inhibitor (**celecoxib**), a nitric-oxide releasing derivative of naproxen (HCT-3012) and naproxen in a model of wound collagen deposition in the rat. Polyvinyl alcohol sponges were implanted subcutaneously in rats. The rats were treated daily for 5 days with the test drugs at equieffective anti-inflammatory doses. Naproxen (10 mg kg(-1)) significantly decreased (45%) collagen deposition at the **wound** site relative to the vehicle-**treated** control group. In contrast, HCT-3012 (14.5 mg kg(-1)) significantly increased (62%) collagen deposition, while **celecoxib** (10 mg kg(-1)) had no effect. Naproxen and HCT-3012 suppressed prostaglandin (PG) E(2) levels at the wound site and whole blood thromboxane synthesis to similar degrees. **Celecoxib** had no significant effect on wound fluid PGE(2) levels, but slightly reduced whole blood thromboxane synthesis (by 17%). COX-1 mRNA and protein were expressed in the wound exudate, the skin surrounding the wound and in normal skin. In contrast, COX-2 mRNA, but not protein, was expressed in wound and normal skin. These results demonstrate that HCT-3012 can significantly enhance collagen deposition at a wound site, despite inhibiting prostaglandin synthesis to the same extent as the parent drug. Nitric oxide-releasing NSAIDs may represent a safer alternative to standard NSAIDs for use as anti-inflammatory and analgesic agents by post-surgery patients.

L5 ANSWER 34 OF 42 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001104375 EMBASE
TITLE: Pharmacology down under in 2000.
AUTHOR: Doggrell S.A.
CORPORATE SOURCE: Dr. S.A. Doggrell, 47 Caronia Crescent, Lynfield, Auckland, New Zealand
SOURCE: Drug News and Perspectives, (2000) 13/10 (634-640).
Refs: 15
ISSN: 0214-0934 CODEN: DNPEED
COUNTRY: Spain
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In December the pharmacologists and toxicologists of Australia and New Zealand get together for their annual scientific meeting, which is made up of pre-meeting workshops followed by invited lectures, symposia and free communications. This year, one of the pre-meeting workshops was on "Animal Models for the Development of Molecular Pharmaceuticals." Symposia included "Models and New **Therapies** for Traumatic Brain **Injury**" and "New Targets for Rheumatoid Arthritis." Novel medicines being developed in Australia revealed at the meeting included potassium channel blockers, C5a receptor agonists and antagonists, brain-derived neurotrophic factor mimetics and AM-36. .COPYRGT. 2000 Prous Science.

L5 ANSWER 35 OF 42 MEDLINE
ACCESSION NUMBER: 2001323701 MEDLINE
DOCUMENT NUMBER: 20479530 PubMed ID: 11028559

TITLE: Blocking prostaglandin E2 after trauma attenuates pro-inflammatory cytokines and improves survival.
AUTHOR: Strong V E; Mackrell P J; Concannon E M; Naama H A; Schaefer P A; Shaftan G W; Stapleton P P; Daly J M
CORPORATE SOURCE: Department of Surgery, New York Presbyterian Hospital-Weill Medical College of Cornell University, New York 10021, USA.
SOURCE: SHOCK, (2000 Sep) 14 (3) 374-9.
Journal code: 9421564. ISSN: 1073-2322.
PUB. COUNTRY: United States
DOCUMENT TYPE: (EVALUATION STUDIES)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010611
Last Updated on STN: 20010611
Entered Medline: 20010607

AB Major injury leads to impaired immune responses and increases the risk of infectious complications. Following trauma, increased prostaglandin E2 (PGE2) levels may be important in immunodysregulation. We hypothesized that blocking PGE2 with **NS-398**, a selective COX-2 inhibitor, during the first 24 h after injury may modify the immune response and protect the host from a subsequent septic challenge. BALB/c mice were given **NS-398** (10 mg/kg) immediately after injury, at 12, and at 24 h after sham injury or trauma (femur fracture and 40% hemorrhage). On day 7 after injury, splenic macrophages were evaluated for cytokine production and COX-2 mRNA. In a separate study mice were injured, then given 3 doses of **NS-398**. After 7 days, cecal ligation and puncture was performed and mice were followed for survival. Traumatized mice given **NS-398** had a significant survival advantage compared with trauma mice alone ($P < 0.001$). Macrophages from traumatized mice showed increased COX-2 mRNA and proinflammatory cytokines compared with controls ($P < 0.05$), whereas **treatment** of **injured** mice with **NS-398** significantly decreased proinflammatory cytokine production ($P < 0.05$) and COX-2 mRNA. Therefore **NS-398** given within 24 h of injury suppressed PGE2 through inhibition of cyclooxygenase, in addition to decreasing proinflammatory cytokines, and providing a survival advantage to the host.

L5 ANSWER 36 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:543206 BIOSIS
DOCUMENT NUMBER: PREV200000543206
TITLE: Acute renal failure under use of COX-2-inhibitor.
AUTHOR(S): Tholl, U. (1); Hermann, R. (1); Anlauf, M. (1)
CORPORATE SOURCE: (1) Medizinische Klinik II, Zentralkranskenhaus Reinkenheide, Bremerhaven Germany
SOURCE: Kidney & Blood Pressure Research, (2000) Vol. 23, No. 3-5, pp. 281-282. print.
Meeting Info.: Congress of Nephrology 2000 Vienna, Austria September 02-05, 2000 Gesellschaft fuer Nephrologie . ISSN: 1420-4096.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L5 ANSWER 37 OF 42 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000102509 EMBASE
TITLE: Management of gastroduodenal ulcers caused by non-steroidal anti-inflammatory drugs.

AUTHOR: Hawkey C.J.
CORPORATE SOURCE: Prof. C.J. Hawkey, Division of Gastroenterology, Queen's Medical Centre, University Hospital, Nottingham, United Kingdom
SOURCE: Bailliere's Best Practice and Research in Clinical Gastroenterology, (2000) 14/1 (173-192).
Refs: 91
ISSN: 1521-6918 CODEN: BBPGFG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Non-steroidal anti-inflammatory drugs (NSAIDs) are a major cause of morbidity and mortality, probably resulting in the death of 1200 patients per annum in the UK. The main mechanism of toxicity involves an inhibition of prostaglandin synthesis that results in mucosal erosion as a result of the abrogation of defence mechanisms. However, acid peptic attack can deepen this initial **injury**. Thus, logical **treatments** include prostaglandin analogues as 'replacement therapy', acid suppression, enteric coating to avoid topical effects and the use of safer NSAIDs, including those that have little or no effect on gastric mucosal prostaglandin synthesis. There is less logic to the strategy of Helicobacter pylori (H. pylori) eradication, and the status of this approach is controversial. Overall, proton pump inhibitors have the best profile of efficacy and side-effects for the healing and prevention of NSAID-associated ulcers. Misoprostol is also effective and appears to be superior to proton pump inhibitors for superficial erosive injury. Early indications are that selective inhibitors of the inducible cyclooxygenase-2 enzyme have little or no effect in causing ulcers. Growing experience with these agents will probably revolutionize the management of patients with arthritic conditions. However, the increasing use of low-dose aspirin for cardiovascular prophylaxis means that gastroenterologists will have to continue to grapple with the problems of NSAID-associated ulcers for some time to come.

L5 ANSWER 38 OF 42 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 2000125786 MEDLINE
DOCUMENT NUMBER: 20125786 PubMed ID: 10657949
TITLE: Cyclooxygenase-2 expression in human pancreatic adenocarcinomas.
AUTHOR: Yip-Schneider M T; Barnard D S; Billings S D; Cheng L; Heilman D K; Lin A; Marshall S J; Crowell P L; Marshall M S; Sweeney C J
CORPORATE SOURCE: Department of Medicine, Department of Biochemistry and Walther Oncology Center, Indiana University School of Medicine, Indianapolis 46202, USA.. myipschn@iupui.edu
SOURCE: CARCINOGENESIS, (2000 Feb) 21 (2) 139-46.
Journal code: 8008055. ISSN: 0143-3334.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000403

AB Cyclooxygenase-2 (COX-2) expression is up-regulated in several types of human cancers and has also been directly linked to carcinogenesis. To investigate the role of COX-2 in pancreatic cancer, we evaluated COX-2 protein expression in primary human pancreatic adenocarcinomas (n = 23) and matched normal adjacent tissue (n = 11) by immunoblot analysis. COX-2 expression was found to be significantly elevated in the pancreatic tumor specimens compared with normal pancreatic tissue. To examine whether the elevated levels of COX-2 protein observed in pancreatic tumors correlated with the presence of oncogenic K-ras, we determined the K-ras mutation status in a subset of the tumors and corresponding normal tissues. The presence of oncogenic K-ras did not correlate with the level of COX-2 protein expressed in the pancreatic adenocarcinomas analyzed. These observations were also confirmed in a panel of human pancreatic tumor cell lines. Furthermore, in the pancreatic tumor cell line expressing the highest level of COX-2 (BxPC-3), COX-2 expression was demonstrated to be independent of Erk1/2 activation. The lack of correlation between COX-2 and oncogenic K-ras expression suggests that Ras activation may not be sufficient to induce COX-2 expression in pancreatic tumor cells and that the aberrant activation of signaling pathways other than Ras may be required for up-regulating COX-2 expression. We also report that the COX inhibitors sulindac, indomethacin and **NS-398** inhibit cell growth in both COX-2-positive (BxPC-3) and COX-2-negative (PaCa-2) pancreatic tumor cell lines. However, suppression of cell growth by indomethacin and **NS-398** was significantly greater in the BxPC-3 cell line compared with the PaCa-2 cell line ($P = 0.004$ and $P < 0.001$, respectively). In addition, the three COX inhibitors reduce prostaglandin E(2) levels in the BxPC-3 cell line. Taken together, our data suggest that COX-2 may play an important role in pancreatic tumorigenesis and therefore be a promising chemotherapeutic target for the **treatment** of **pancreatic** cancer.

L5 ANSWER 39 OF 42 MEDLINE
ACCESSION NUMBER: 2000417910 MEDLINE
DOCUMENT NUMBER: 20409661 PubMed ID: 10953541
TITLE: Selective COX-2 inhibitors and gastrointestinal mucosal **injury**: pharmacological and **therapeutic** considerations.
AUTHOR: Dajani E Z; Agrawal N M
CORPORATE SOURCE: International Drug Development Consultants Corporation, Long Grove, IL 60047-9532, USA.
SOURCE: JOURNAL OF THE ASSOCIATION FOR ACADEMIC MINORITY PHYSICIANS, (2000) 11 (2-3) 28-31. Ref: 22
Journal code: 9113765. ISSN: 1048-9886.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000915
Last Updated on STN: 20000915
Entered Medline: 20000906

AB It is well recognized that nonsteroidal antiinflammatory drugs (NSAIDs) induce gastrointestinal (GI) ulcerations, perforation and bleeding, which clearly limit their therapeutic value. The recent introduction of NSAIDs with selective cyclooxygenase-2 (COX-2) inhibitory effect is a major pharmacologic milestone in therapeutics. Selective COX-2 inhibitors exhibit considerable dissociation between their antiinflammatory/analgesic action and their GI toxicity. However, from a therapeutic consideration,

there are still several unresolved and confusing issues with these drugs such as: the pharmacologic classification of the COX-2 selectivity; therapeutic value as antirheumatic/analgesic drugs; potential toxicity in patients at risk for the development of ulcer-related complications or patients with inflammatory bowel disease and potential renal toxicity. Although existing clinical efficacy studies with **celecoxib** and rofecoxib, two selective COX-2 inhibitors, were associated with considerably lower ulcerogenic rates when compared with nonselective NSAIDs, there are no long term outcome studies with these drugs similar to the MUCOSA trial performed with misoprostol. Furthermore, the selectivity of COX-2 inhibitors appears to be specific to the stomach and duodenum but not the kidney. While awaiting additional long term studies with selective COX-2 inhibitors, we recommend instituting prophylactic therapy with misoprostol in patients at risk for the development of ulcer related complications. In conclusion, we believe that the introduction of selective COX-2 inhibitors will revolutionize the treatment of pain and inflammation. However, additional basic and clinical studies are required to address the pharmacologic and therapeutic uncertainties for this class of drugs.

L5 ANSWER 40 OF 42 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 1999413493 MEDLINE
DOCUMENT NUMBER: 99413493 PubMed ID: 10485483
TITLE: Increased cyclooxygenase-2 expression in human pancreatic carcinomas and cell lines: growth inhibition by nonsteroidal anti-inflammatory drugs.
AUTHOR: Molina M A; Sitja-Arnau M; Lemoine M G; Frazier M L; Sinicrope F A
CORPORATE SOURCE: Department of Epidemiology, The University of Texas M. D. Anderson Cancer Center, Houston 77030, USA.
CONTRACT NUMBER: CA 16672 (NCI)
CA 70759 (NCI)
SOURCE: CANCER RESEARCH, (1999 Sep 1) 59 (17) 4356-62.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991012
Last Updated on STN: 20000303
Entered Medline: 19990930

AB Cyclooxygenase (COX)-2 mRNA and protein expression were found to be frequently elevated in human pancreatic adenocarcinomas and cell lines derived from such tumors. Immunohistochemistry demonstrated cytoplasmic COX-2 expression in 14 of 21 (67%) pancreatic carcinomas. The level of COX-2 mRNA was found to be elevated in carcinomas, relative to histologically normal pancreas from a healthy individual, as assessed by reverse transcription-PCR. COX-2 protein expression was detected by the Western blot assay in three of five pancreatic carcinoma cell lines (BxPC-3, Capan-1, and MDAPanc-3), whereas COX-1 protein was detected in two of the five cell lines (BxPC-3 and Capan-1). Increased levels of COX-2 mRNA were found in four of five cell lines, and only in PANC-1 cells was the low level of transcript comparable to that in the normal pancreas. The level of COX-2 mRNA was positively correlated with the differentiation status of the tumor of origin for each cell line, COX-2 protein expression was up-regulated by epidermal growth factor when the cells were grown in absence of serum. Finally, two nonsteroidal anti-inflammatory drugs, sulindac sulfide and **NS398**, produced a dose-dependent inhibition of cell proliferation in all pancreatic cell lines tested. No correlation

was found between the level of COX-2 or COX-1 expression and the extent of growth inhibition. Treatment of BxPC-3 cells with sulindac sulfide and **NS398** resulted in an induction of COX-2 expression. Our findings indicate that COX-2 up-regulation is a frequent event in pancreatic cancers and suggest that nonsteroidal anti-inflammatory drugs may be useful in the chemoprevention and **therapy** of **pancreatic** carcinoma.

L5 ANSWER 41 OF 42 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999315270 EMBASE
TITLE: Novel therapeutic strategies.
AUTHOR: Worker C.
CORPORATE SOURCE: C. Worker, Current Drugs Ltd, Middlesex House, 34-42 Cleveland Street, London W1P 6LB, United Kingdom. charlotte@cursci.co.uk
SOURCE: IDrugs, (1999) 2/9 (848-852).
ISSN: 1369-7056 CODEN: IDRUFN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Of the many sessions during the first day of the EPHAR meeting, several interesting topics emerged. Among these were a number of presentations investigating novel anti-inflammatory targets, including the search for a selective COX-2 inhibitor and the potential of cytokines/cytokine receptor targets (eg TNF.alpha.) as treatments for rheumatoid arthritis (RA) and other chronic inflammatory conditions. Recent advances in the understanding of the pathogenesis of diabetes and obesity have highlighted the need for a multi-therapeutic approach to treatment; several drugs in preclinical investigations were highlighted. Attention was drawn to the potential of AMPA/kainate receptors, historically investigated for the treatment of neurodegenerative disease, which are now showing promise as anti-ischemic therapeutics. Many novel therapeutics strategies were discussed in detail, including the CCK-B antagonists with considerable anxiolytic potential, mitochondrial mechanisms as targets for the **treatment** of brain **injury** and the use of stress-activated proteins in anti-ischemic research.

L5 ANSWER 42 OF 42 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 1998380907 MEDLINE
DOCUMENT NUMBER: 98380907 PubMed ID: 9715175
TITLE: Cyclooxygenase-2 inhibitor **NS-398** improves survival and restores leukocyte counts in burn infection.
AUTHOR: Shoup M; He L K; Liu H; Shankar R; Gamelli R
CORPORATE SOURCE: Burn and Shock Trauma Institute, Loyola University Medical Center, Maywood, IL, USA.
CONTRACT NUMBER: F32 GM 18519 (NIGMS)
RO1-42577
RO1-GM56424 (NIGMS)
SOURCE: JOURNAL OF TRAUMA, (1998 Aug) 45 (2) 215-20; discussion 220-1.
Journal code: 0376373. ISSN: 0022-5282.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199809

ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980910

AB BACKGROUND: Cyclooxygenase-2 (COX-2) is a key enzyme in the production of prostaglandin E2 (PGE2) from activated macrophages. PGE2 is increased during trauma and sepsis and has been implicated as a negative immunomodulator. The objective of this study was to determine the therapeutic benefits of a COX-2 inhibitor (**NS-398**) on survival and leukocyte production in a murine model of burn sepsis. METHODS: To determine the in vitro ability of **NS-398** to inhibit macrophage production of PGE2, peritoneal elicited macrophages were stimulated for 18 hours with medium alone, endotoxin (ETX) (1 mumol/L), or ETX plus **NS-398** (0.3 mumol/L). Macrophage supernatant PGE2 levels were determined by an enzyme immunoassay. To test the in vivo efficacy of **NS-398**, mice subjected to a 15% dorsal scald burn plus 1,000 colony-forming units of topical Pseudomonas aeruginosa received either 10 mg/kg **NS-398** intraperitoneally or placebo 4 to 6 hours after infection and twice daily for 3 days. Survival was measured up to 14 days, and circulating white blood cell (WBC) count and absolute neutrophil count (ANC) were determined 3 days after injury. RESULTS: Macrophage PGE2 production was significantly increased in the ETX-treated group compared with the medium-alone group, and this increase was completely normalized with the addition of **NS-398**. **NS-398** also augmented WBC count (4,288 +/- 649 vs. 7,866 +/- 435 per mm3; p < 0.01) and ANC (1,068 +/- 255 vs. 3,663 +/- 474 per mm3) after burn infection and attenuated macrophage depression of hematopoietic proliferation. Finally, **NS -398 treatment** significantly improved survival after **burn** infection, from 0 to 45.5%. CONCLUSION: Inhibition of the COX-2 isoform of cyclooxygenase with **NS-398** inhibited macrophage PGE2 production, restored ANC, and improved survival during burn infection. **NS-398**, therefore, has potential therapeutic benefits in septic patients who have developed neutropenia.

FILE 'MEDLINE' ENTERED AT 16:36:37 ON 03 SEP 2002
L6 12316 SEA ABB=ON PLU=ON (CYCLOOXYGENASE INHIBITORS OR PROSTAGLANDIN -ENDOPEROXIDE SYNTHASE)/CT

L7 117 SEA ABB=ON PLU=ON L6 AND (WOUNDS AND INJURIES OR PANCREATITIS OR BURNS OR SEPSIS)/CT
L8 24 SEA ABB=ON PLU=ON L7 AND (THERAPY OR THERAPEUTIC USE)/CT
D L8 IBIB ABS 1-24

=> d l8 ibib abs 1-24

L8 ANSWER 1 OF 24 MEDLINE
ACCESSION NUMBER: 2002308621 MEDLINE
DOCUMENT NUMBER: 21992584 PubMed ID: 11996850
TITLE: Protective role of cyclooxygenase (COX) inhibitors in burn-induced intestinal and liver damage.
AUTHOR: Oktar Berna K; Cakir Baris; Mutlu Nilgun; Celikel Cigdem; Alican Inci
CORPORATE SOURCE: Department of Physiology, School of Medicine, Marmara University, 81326 Haydarpasa, Istanbul, Turkey.
SOURCE: BURNS, (2002 May) 28 (3) 209-14.
Journal code: 8913178. ISSN: 0305-4179.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020611
Last Updated on STN: 20020803
Entered Medline: 20020802

AB The aim of this study was to investigate the role of cyclooxygenase (COX) inhibition in intestinal motility and in the extent of tissue injury of the small intestine and liver with the use of various COX inhibitors. Wistar albino rats were exposed to 90 degrees C water bath for 10s. The intestinal transit index decreased compared to control group and treatment with nimesulide (NIM; 10mg/kg, subcutaneously) or piroxicam (Pir; 5mg/kg, orogastrically) reversed this effect significantly. The intestinal and liver glutathione levels showed a significant decrease in the burn group compared to sham ($P<0.001$ and $P<0.05$, respectively). Decrease in intestinal glutathione level was reversed by NIM or Pir treatment ($P<0.01$ and $P<0.01$, respectively), whereas all drugs tested were effective in reversing low liver glutathione level. The MPO activity in intestinal segments were significantly high in burned animals compared to sham. All test drugs reversed this effect but ketorolac (Ket; 3mg/kg, orogastrically) was the most effective one. The liver samples characterized by sinusoidal dilatation and pericentral atrophy in burn group were protected by treatment with Ket or Pir ($P<0.05$). Plasma ALT and AST activities were markedly high in this burn group compared to sham ($P<0.0001$ and $P<0.001$, respectively). None of the agents reversed these high enzyme activities. These data suggest that not only COX-2 but also COX-1 inhibition is required for protection against inflammatory changes in liver and small intestine following burn injury.

L8 ANSWER 2 OF 24 MEDLINE
ACCESSION NUMBER: 2002276489 MEDLINE
DOCUMENT NUMBER: 22011633 PubMed ID: 12016091
TITLE: A cyclooxegenase-2 inhibitor impairs ligament healing in the rat.
AUTHOR: Ekman Evan F
SOURCE: AMERICAN JOURNAL OF SPORTS MEDICINE, (2002 May-Jun) 30 (3) 457; discussion 457.
Journal code: 7609541. ISSN: 0363-5465.
PUB. COUNTRY: United States
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020518
Last Updated on STN: 20020712
Entered Medline: 20020710

L8 ANSWER 3 OF 24 MEDLINE
ACCESSION NUMBER: 2002229233 MEDLINE
DOCUMENT NUMBER: 21962465 PubMed ID: 11964481
TITLE: Role of prostacyclin in the cardiovascular response to thromboxane A2.
COMMENT: Comment in: Science. 2002 Apr 19;296(5567):474-5
AUTHOR: Cheng Yan; Austin Sandra C; Rocca Bianca; Koller Beverly H; Coffman Thomas M; Grosser Tilo; Lawson John A; FitzGerald Garret A
CORPORATE SOURCE: Center for Experimental Therapeutics, 153 Johnson Pavilion, 3620 Hamilton Walk, University of Pennsylvania School of Medicine, Philadelphia, PA 19104-6084, USA.
CONTRACT NUMBER: HL 54500 (NHLBI)

HL 62250 (NHLBI)
SOURCE: SCIENCE, (2002 Apr 19) 296 (5567) 539-41.
Journal code: 0404511. ISSN: 1095-9203.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020423
Last Updated on STN: 20020514
Entered Medline: 20020513

AB Thromboxane (Tx) A2 is a vasoconstrictor and platelet agonist. Aspirin affords cardioprotection through inhibition of TxA2 formation by platelet cyclooxygenase (COX-1). Prostacyclin (PGI2) is a vasodilator that inhibits platelet function. Here we show that injury-induced vascular proliferation and platelet activation are enhanced in mice that are genetically deficient in the PGI2 receptor (IP) but are depressed in mice genetically deficient in the TxA2 receptor (TP) or treated with a TP antagonist. The augmented response to vascular injury was abolished in mice deficient in both receptors. Thus, PGI2 modulates platelet-vascular interactions in vivo and specifically limits the response to TxA2. This interplay may help explain the adverse cardiovascular effects associated with selective COX-2 inhibitors, which, unlike aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), inhibit PGI2 but not TxA2.

L8 ANSWER 4 OF 24 MEDLINE
ACCESSION NUMBER: 2001520273 MEDLINE
DOCUMENT NUMBER: 21411264 PubMed ID: 11520726
TITLE: Effect of endotoxin on ventilation and breath variability: role of cyclooxygenase pathway.
AUTHOR: Preas H L 2nd; Jubran A; Vandivier R W; Reda D; Godin P J; Banks S M; Tobin M J; Suffredini A F
CORPORATE SOURCE: Critical Care Medicine Department, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland, USA.
SOURCE: AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, (2001 Aug 15) 164 (4) 620-6.
Journal code: 9421642. ISSN: 1073-449X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010925
Last Updated on STN: 20011015
Entered Medline: 20011011

AB To evaluate the effects of endotoxemia on respiratory controller function, 12 subjects were randomized to receive endotoxin or saline; six also received ibuprofen, a cyclooxygenase inhibitor, and six received placebo. Administration of endotoxin produced fever, increased respiratory frequency, decreased inspiratory time, and widened alveolar-arterial oxygen tension gradient (all $p < \text{or} = 0.001$); these responses were blocked by ibuprofen. Independent of ibuprofen, endotoxin produced dyspnea, and it increased fractional inspiratory time, minute ventilation, and mean inspiratory flow (all $p < \text{or} = 0.025$). Endotoxin altered the autocorrelative behavior of respiratory frequency by increasing its autocorrelation coefficient at a lag of one breath, the number of breath lags with significant serial correlations, and its correlated fraction

(all p < 0.05); these responses were blocked by ibuprofen. Changes in correlated behavior of respiratory frequency were related to changes in arterial carbon dioxide tension (r = 0.86; p < 0.03). Endotoxin decreased the oscillatory fraction of inspiratory time in both the placebo (p < 0.05) and ibuprofen groups (p = 0.06). In conclusion, endotoxin produced increases in respiratory motor output and dyspnea independent of fever and symptoms, and it curtailed the freedom to vary respiratory timing-a response that appears to be mediated by the cyclooxygenase pathway.

L8 ANSWER 5 OF 24 MEDLINE
ACCESSION NUMBER: 2001474133 MEDLINE
DOCUMENT NUMBER: 21409613 PubMed ID: 11517779
TITLE: [Multiple organ failure].
Problema poliorgannoi nedostatochnosti.
AUTHOR: Grinev M V; Golubeva A V
SOURCE: VESTNIK KHIRURGII IMENI I. I. GREKOVA, (2001) 160 (3) 110-4. Ref: 53
Journal code: 0411377. ISSN: 0042-4625.
PUB. COUNTRY: Russia: Russian Federation
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20010827
Last Updated on STN: 20020228
Entered Medline: 20020227

L8 ANSWER 6 OF 24 MEDLINE
ACCESSION NUMBER: 1999388795 MEDLINE
DOCUMENT NUMBER: 99388795 PubMed ID: 10459503
TITLE: Indomethacin reduces the skin thermal damage in hyperthermic treatment of experimental malignant tumors.
AUTHOR: Ostapenko V V; Akagi K; Yamamoto I; Tanaka Y
CORPORATE SOURCE: Department of Radiology, Kansai Medical University, Osaka, Japan.. valentin@sun-inet.or.jp
SOURCE: IN VIVO, (1999 May-Jun) 13 (3) 255-7.
Journal code: 8806809. ISSN: 0258-851X.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991101
Last Updated on STN: 19991101
Entered Medline: 19991015

AB Indomethacin (Ind), an inhibitor of prostaglandin synthesis, was previously shown to increase the thermosensitivity of murine tumors. The potency of drug to modify the thermal response of murine skin has been evaluated in mice heated in water bath at 44 degrees C for 30, 60 and 90 min. Ind was administered subcutaneously (s.c.) at dose of 5 mg/kg body weight (b.w.) 1.5 h before heating. The mouse foot skin reactions (FSR) were assessed using the scoring system of Urano et al (1979). The severity of skin thermal damage was decreased markedly by Ind. At the time when heating of the control group at 44 degrees C for 60 min resulted in the irreversible FSR in some mice, pretreatment with Ind before heating lead to the complete recovery from the heat damage in all mice. Similarly, after heating at 44 degrees C for 90 min, the degree of FSR was diminished by Ind from score 4.5 to score 2. It is concluded that Ind selectively

protected normal skin during the hyperthermic treatment. Further clinical study is warranted.

L8 ANSWER 7 OF 24 MEDLINE
ACCESSION NUMBER: 1999349523 MEDLINE
DOCUMENT NUMBER: 99349523 PubMed ID: 10422661
TITLE: Synergistic antiallodynic effects of spinal morphine with ketorolac and selective COX1- and COX2-inhibitors in nerve-injured rats.
AUTHOR: Lashbrook J M; Ossipov M H; Hunter J C; Raffa R B; Tallarida R J; Porreca F
CORPORATE SOURCE: Department of Pharmacology, The University of Arizona Health Sciences Center, Tucson 85724-5050, USA.
CONTRACT NUMBER: DA 08657 (NIDA)
SOURCE: PAIN, (1999 Jul) 82 (1) 65-72.
Journal code: 7508686. ISSN: 0304-3959.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 20000303
Entered Medline: 19990923

AB The possible role of spinal prostanoids in the tactile allodynia and thermal hyperalgesia associated with an experimental model of neuropathic pain was investigated. Neuropathic pain was induced by tight ligation of the L5 and L6 spinal nerves. Tactile allodynia was assessed 7 days after the surgery by measuring hindpaw withdrawal threshold to probing with von Frey filaments. Thermal hyperalgesia and nociception were determined by the 52 degrees C warm-water tail-flick test and by applying radiant heat to the plantar aspect of the hindpaw ipsilateral to the ligation. Minimal antiallodynic effect was produced by intrathecal (i.th.) administration of ketorolac or morphine up to the highest testable dose (100 microg) or by the (R)- or (S)-enantiomers of ketorolac (up to 6 microg) when administered alone. However, i.th. administration of a fixed ratio (1:1) of morphine plus racemic ketorolac or of morphine plus the (S)-enantiomer of ketorolac (S-ketorolac) produced a dose- and time-related antiallodynic effect: ED50 114 +/- 35.9 microg (total dose) for morphine plus ketorolac and 70.5 +/- 21.0 microg (total dose) for morphine plus S-ketorolac. The combination of i.th. morphine plus the (R)-enantiomer of ketorolac (R-ketorolac) (up to 200 microg total dose) was without effect. Similar antiallodynic activity was obtained for the co-administration of i.th. morphine and intravenous (i.v.) racemic ketorolac. In order to investigate the role of cyclooxygenase (COX) isozymes, relatively selective COX1 (piroxicam) and COX2 N-[2-cyclohexyloxy-4-nitrophenyl] metanesulfonamide (NS-398) inhibitors were administered i.th. (60 microg) alone or together with i.th. morphine. Piroxicam, NS-398, morphine and vehicle (90% DMSO) were without significant antiallodynic effect when administered alone, but moderate antiallodynic effects were produced by i.th. administration of fixed ratio (1:1) combinations of morphine with 60 microg each (highest soluble dose) of piroxicam (%MPE = 40.8 +/- 10.2) or NS-398 (%MPE = 32.4 +/- 9.5). Further, the combined i.th. administration of morphine, piroxicam and NS-398 in fixed 1:1:1 ratio (60 microg each) resulted in a supraadditive antiallodynic effect (%MPE = 70.4 +/- 10.8). Finally, morphine, but not ketorolac, given i.th. produced dose-dependent anti nociception in either the tail-flick or the paw-flick tests. However, there was no synergy between morphine and ketorolac against thermal nociception in either of the tests. These findings suggest that spinal prostanoids produced via both COX1 and COX2 pathways may play a role in

neuropathic pain states and suggest the clinical utility of opioid plus COX-inhibitor combination therapy.

L8 ANSWER 8 OF 24 MEDLINE
ACCESSION NUMBER: 1999268721 MEDLINE
DOCUMENT NUMBER: 99268721 PubMed ID: 10338399
TITLE: Prostanoids: early mediators in the secondary injury that develops after unilateral pulmonary contusion.
AUTHOR: Davis K A; Fabian T C; Croce M A; Proctor K G
CORPORATE SOURCE: Department of Surgery, University of Tennessee, Memphis, USA.. kdavis3@luc.edu
SOURCE: JOURNAL OF TRAUMA, (1999 May) 46 (5) 824-31; discussion 831-2.
Journal code: 0376373. ISSN: 0022-5282.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990618
Last Updated on STN: 19990618
Entered Medline: 19990608

AB BACKGROUND: We have previously shown a sequence of events after unilateral pulmonary contusion that suggests the release of blood-borne prostanoid mediators and that culminates in refractory bilateral pulmonary failure. PURPOSE: To determine the role of platelet-derived thromboxane and endothelial-derived prostacyclin in the primary and secondary injury after unilateral blunt chest trauma, and to determine whether pretreatment with the cyclooxygenase inhibitor indomethacin alters the progression of secondary injury. METHODS: Anesthetized, ventilated (FIO2 = 0.50) pigs received a unilateral, blunt injury to the right thorax (n = 20) or sham injury (n = 5) and were monitored for 24 hours. Either indomethacin (5 mg/kg i.v.; n = 10) or its saline vehicle (n = 10) were administered 15 minutes before injury. Serial bronchoalveolar lavages of each lung were analyzed for protein and neutrophil (polymorphonuclear neutrophil (PMN)) content. RESULTS: Contusion caused profound hypoxemia; PaO2 partially recovered within 1 hour of injury to 50% of baseline. Thereafter, worsening hypoxemia required positive end-expiratory pressure. With indomethacin compared with vehicle, PaO2 was higher at any given level of positive end-expiratory pressure ($p < 0.05$). There was an early increase in serial bronchoalveolar lavage protein on the injured side (peak at 2 hours), with a delayed pulmonary capillary leak on the contralateral side (peak at 6 hours), which correlated with increasing PMN infiltration; this was reduced by 40 to 60% with indomethacin ($p < 0.05$). Thromboxane peaked within 1 hour after contusion at 800% baseline, then fell off rapidly. This peak preceded the maximal increase in permeability and was completely blocked by indomethacin. Prostacyclin slowly rose to 300% baseline by 3 hours and remained elevated; this change was blocked by indomethacin for 18 hours. CONCLUSIONS: Contusion of the right thorax induced a delayed pulmonary capillary leak in the left lung, which reflects a progressive secondary inflammatory response. Elevations in thromboxane and prostacyclin preceded progressive bilateral PMN infiltration. Indomethacin blocked thromboxane and prostacyclin and attenuated, but did not prevent, the progression to pulmonary failure. Overall, these data suggest that prostanoids are released soon after unilateral contusion and initiate an inflammatory response in both lungs that is sustained by PMN infiltration.

L8 ANSWER 9 OF 24 MEDLINE
ACCESSION NUMBER: 1999015068 MEDLINE
DOCUMENT NUMBER: 99015068 PubMed ID: 9798334

TITLE: The effects of prostaglandin E2 indomethacin & Ginkgo biloba extract on resistance to experimental sepsis.
AUTHOR: Canturk N Z; Utkan N Z; Canturk Z; Yenisey C; Yildirir C; Dulger M
CORPORATE SOURCE: Kocaeli University, Faculty of Medicine, Department of Surgery, Kocaeli, Turkey.
SOURCE: INDIAN JOURNAL OF MEDICAL RESEARCH, (1998 Sep) 108 88-92. Journal code: 0374701. ISSN: 0971-5916.
PUB. COUNTRY: India
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981117

AB We investigated the effect of 16,16-dimethyl prostaglandin E2 indomethacin and Ginkgo biloba extract on the survival in two experimental sepsis models in rats due to administration of 1 x 10(7) cfu and 1 x 10(9) cfu Escherichia coli. Animals in each model were then randomly divided (10/group) into four groups, administered saline, indomethacin, G. biloba extract and prostaglandin E2 respectively. When compared, there was no significant difference in the survival period between the two sepsis models (P > 0.05). The best survival rate was observed in the PGE2-administered animals in the first major model (P < 0.05). Indomethacin appeared not to decrease the mortality rates. There was no significant difference in PGE2 levels between two sepsis models (P > 0.05). Our results suggest that elevated prostaglandin E2 levels following major trauma are not responsible for the postinjury increased susceptibility to infectious complications. Our observations should also discourage aggressive use of cyclo-oxygenase inhibitors for protection against infectious complications after major trauma.

L8 ANSWER 10 OF 24 MEDLINE
ACCESSION NUMBER: 1998380907 MEDLINE
DOCUMENT NUMBER: 98380907 PubMed ID: 9715175
TITLE: Cyclooxygenase-2 inhibitor NS-398 improves survival and restores leukocyte counts in burn infection.
AUTHOR: Shoup M; He L K; Liu H; Shankar R; Gamelli R
CORPORATE SOURCE: Burn and Shock Trauma Institute, Loyola University Medical Center, Maywood, IL, USA.
CONTRACT NUMBER: F32 GM 18519 (NIGMS)
RO1-42577
RO1-GM56424 (NIGMS)
SOURCE: JOURNAL OF TRAUMA, (1998 Aug) 45 (2) 215-20; discussion 220-1. Journal code: 0376373. ISSN: 0022-5282.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980910

AB BACKGROUND: Cyclooxygenase-2 (COX-2) is a key enzyme in the production of prostaglandin E2 (PGE2) from activated macrophages. PGE2 is increased during trauma and sepsis and has been implicated as a negative immunomodulator. The objective of this study was to determine the therapeutic benefits of a COX-2 inhibitor (NS-398) on survival and

leukocyte production in a murine model of burn sepsis. METHODS: To determine the in vitro ability of NS-398 to inhibit macrophage production of PGE2, peritoneal elicited macrophages were stimulated for 18 hours with medium alone, endotoxin (ETX) (1 mumol/L), or ETX plus NS-398 (0.3 mumol/L). Macrophage supernatant PGE2 levels were determined by an enzyme immunoassay. To test the in vivo efficacy of NS-398, mice subjected to a 15% dorsal scald burn plus 1,000 colony-forming units of topical Pseudomonas aeruginosa received either 10 mg/kg NS-398 intraperitoneally or placebo 4 to 6 hours after infection and twice daily for 3 days. Survival was measured up to 14 days, and circulating white blood cell (WBC) count and absolute neutrophil count (ANC) were determined 3 days after injury. RESULTS: Macrophage PGE2 production was significantly increased in the ETX-treated group compared with the medium-alone group, and this increase was completely normalized with the addition of NS-398. NS-398 also augmented WBC count (4,288 +/- 649 vs. 7,866 +/- 435 per mm3; $p < 0.01$) and ANC (1,068 +/- 255 vs. 3,663 +/- 474 per mm3) after burn infection and attenuated macrophage depression of hematopoietic proliferation. Finally, NS-398 treatment significantly improved survival after burn infection, from 0 to 45.5%. CONCLUSION: Inhibition of the COX-2 isoform of cyclooxygenase with NS-398 inhibited macrophage PGE2 production, restored ANC, and improved survival during burn infection. NS-398, therefore, has potential therapeutic benefits in septic patients who have developed neutropenia.

L8 ANSWER 11 OF 24 MEDLINE
ACCESSION NUMBER: 1998206532 MEDLINE
DOCUMENT NUMBER: 98206532 PubMed ID: 9546456
TITLE: Indomethacin versus radiation therapy for prophylaxis against heterotopic ossification in acetabular fractures: a randomised, prospective study.
AUTHOR: Moore K D; Goss K; Anglen J O
CORPORATE SOURCE: University of Missouri Hospital and Clinics, Columbia 65212, USA.
SOURCE: JOURNAL OF BONE AND JOINT SURGERY. BRITISH VOLUME, (1998 Mar) 80 (2) 259-63.
Journal code: 0375355. ISSN: 0301-620X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980507
Last Updated on STN: 20000303
Entered Medline: 19980430

AB We report a prospective, randomised, blinded clinical comparison of the use of indomethacin or radiation therapy for the prevention of heterotopic ossification (HO) in 75 adults who had open reduction and internal fixation of acetabular fractures through either a Kocher-Langenbeck, a combined ilioinguinal and Kocher-Langenbeck, or an extended iliofemoral approach. Indomethacin, 25 mg, was given three times daily for six weeks. Radiation with 800 cGy was delivered within three days of operation. Plain radiographs were reviewed and given Brooker classification scores by three independent observers who were unaware of the method of prophylaxis. One patient died from unrelated causes and two were lost to follow-up, leaving 72, 33 in the radiation group and 39 in the indomethacin group, available for evaluation at a mean of 12 months (6 to 48). There was no significant difference in the two groups in terms of age, gender, injury severity score, estimated blood loss, delay to surgery, head injury, presence of

femoral head dislocation, or operating time, and no complications due to either method of treatment. The final extent of HO was already present by six weeks in all patients who were followed up. Three patients in the radiation group and five who received indomethacin developed HO of Brooker grade III. Two patients in the indomethacin group developed Brooker IV changes; both had failed to receive proper doses of the drug. Cochran-Armitage analysis showed no significant difference between the two treatment groups as regards the formation of HO. Indomethacin and single-dose radiation therapy are both safe and effective for the prevention of HO after operation for acetabular fractures. Radiation therapy is, however, approximately 200 times more expensive than indomethacin therapy at our institution and has other risks.

L8 ANSWER 12 OF 24 MEDLINE
ACCESSION NUMBER: 1998172080 MEDLINE
DOCUMENT NUMBER: 98172080 PubMed ID: 9511090
TITLE: Therapeutic options directed against platelet activating factor, eicosanoids and bradykinin in sepsis.
AUTHOR: Fink M P
CORPORATE SOURCE: Department of Surgery, Beth Israel Deaconess Medical Center, Boston, MA, USA.
CONTRACT NUMBER: GM3763 (NIGMS)
SOURCE: JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, (1998 Jan) 41 Suppl A 81-94. Ref: 210
Journal code: 7513617. ISSN: 0305-7453.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980416
Last Updated on STN: 19980416
Entered Medline: 19980408

AB Various autacoids, including the eicosanoids, platelet activating factor (PAF) and bradykinin, have been implicated in the pathogenesis of sepsis and septic shock. The precise role of these compounds as mediators of the diffuse inflammatory state characteristic of sepsis remains to be determined, but, in animal models, beneficial effects have been observed as a result of treatment with various inhibitors of eicosanoid biosynthesis or antagonists of PAF or bradykinin receptors. To date, however, it has been impossible to translate these encouraging results from animal models into convincingly positive results in the clinical setting.

L8 ANSWER 13 OF 24 MEDLINE
ACCESSION NUMBER: 1998129425 MEDLINE
DOCUMENT NUMBER: 98129425 PubMed ID: 9469523
TITLE: Effect of NSAID administration on tissue levels of immunoreactive prostaglandin E2, leukotriene B4, and (S)-flurbiprofen following extraction of impacted third molars.
AUTHOR: Roszkowski M T; Swift J Q; Hargreaves K M
CORPORATE SOURCE: Division of Oral and Maxillofacial Surgery, University of Minnesota, School of Dentistry, Minneapolis 55455, USA.
CONTRACT NUMBER: K16DE0027 (NIDCR)
P30DE09737 (NIDCR)
R01DE11277 (NIDCR)
+

SOURCE: PAIN, (1997 Dec) 73 (3) 339-45.
Journal code: 7508686. ISSN: 0304-3959.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980407
Last Updated on STN: 20000303
Entered Medline: 19980324

AB Post-operative pain and inflammation are frequently managed with non-steroidal anti-inflammatory drugs (NSAIDs). Despite the prevalence of their use, however, relatively little is known about in vivo tissue concentrations of inflammatory mediators at the site of tissue injury and their modulation by NSAIDs. This study compares the effect of oral administration of the NSAID flurbiprofen, to placebo, on tissue levels of immunoreactive prostaglandin E2 (iPGE2), leukotriene B4 (iLTB4), and (S)-flurbiprofen within the surgical wound using implanted microdialysis probes in the dental impaction pain model. Twenty-four healthy patients in need of extraction of partial to complete bony mandibular third molars were recruited for this randomized, double-blind, placebo-controlled study. Following pre-operative administration of N2O/O2, midazolam i.v., and regional block anesthesia with 3% mepivacaine, each patient underwent surgical removal of their impacted third molars. Immediately following completion of the surgery, two semi-permeable microdialysis probes (3 kDa molecular weight cut-off) were implanted into each mandibular surgical site. Patients were taken to a recovery room and microdialysis samples and patient pain reports (visual analog scale, VAS) were collected at 30 min intervals for 4 h. Patients randomly received either flurbiprofen (200 mg orally) or placebo at the onset of post-operative pain. Dialysate samples were collected, frozen, and later assayed for iPGE2, iLTB4, and (S)-flurbiprofen levels. Results of this study show that flurbiprofen decreased post-operative pain by approximately 70% compared to placebo-treated patients ($P < 0.001$). During the 4 h post-operative timecourse of this study, flurbiprofen treatment significantly reduced peak tissue levels of iPGE2 (9.2 +/- 2.6 vs. 0.4 +/- 0.15 nM; $P < 0.001$), without having a significant effect on peak tissue levels of iLTB4 (2.5 +/- 1.4 vs. 1.49 +/- 0.86 nM) compared to placebo treatment. Levels of (S)-flurbiprofen significantly increased within the surgical wound exceeding therapeutic levels by 60 min after administration. Flurbiprofen is able to significantly suppress the local production of iPGE2 and provide significant analgesic efficacy without altering iLTB4 tissue levels in this model of acute post-operative inflammatory pain. These data indicate that NSAIDs selectively alter eicosanoid levels within surgical wound and evoke analgesia at time points coincident with elevated wound levels of the drug. The combined use of microdialysis probes in awake patients who provide simultaneous pain reports may offer insight into peripheral mechanisms of inflammatory mediator release and pain.

L8 ANSWER 14 OF 24 MEDLINE
ACCESSION NUMBER: 97203763 MEDLINE
DOCUMENT NUMBER: 97203763 PubMed ID: 9051335
TITLE: Ketoprofen and carotico-cavernous fistula.
AUTHOR: Burton E A; Jamieson D G
CORPORATE SOURCE: University Department of Neurology, Queen Elizabeth Hospital, Birmingham, UK.
SOURCE: CEPHALALGIA, (1997 Feb) 17 (1) 40-1.
Journal code: 8200710. ISSN: 0333-1024.

PUB. COUNTRY: Norway
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970507
Last Updated on STN: 19970507
Entered Medline: 19970429

AB Whilst treating a patient with traumatic direct carotico-cavernous fistula, pain relief was difficult to achieve. Adequate doses of ibuprofen and codeine were ineffective, but single doses of ketoprofen alleviated pain in a reproducible manner. Although similar in analgesic efficacy to codeine, and a potent inhibitor of cyclooxygenase like ibuprofen, ketoprofen has other actions which may account for the differential response seen. This observation may help elucidate the nature of local mediators involved in the pathogenesis of vascular headache pain.

L8 ANSWER 15 OF 24 MEDLINE
ACCESSION NUMBER: 96384170 MEDLINE
DOCUMENT NUMBER: 96384170 PubMed ID: 8792067
TITLE: Pharmacotherapy of sepsis.
AUTHOR: Weikert L F; Bernard G R
CORPORATE SOURCE: Division of Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA.
CONTRACT NUMBER: HL 07123 (NHLBI)
HL 19153 (NHLBI)
HL 43167 (NHLBI)
SOURCE: CLINICS IN CHEST MEDICINE, (1996 Jun) 17 (2) 289-305. Ref: 157
Journal code: 7907612. ISSN: 0272-5231.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961120

AB During the past few years, many promising new agents for the treatment of sepsis have been studied to varying degrees in vitro as well as in vivo in animals and humans. Although there is a relative plethora of animal data, full-scale clinical trials of size sufficient to yield clear answers are rare. Many of the agents appear to hold promise based on preliminary data in animals or from small human studies, and some are undergoing multicenter clinical investigation. At present, however, none of the agents discussed clearly has shown survival benefit when administered to patients with sepsis. Certainly, none can be recommended as standard therapy, and others such as glucocorticoids should be avoided. Nevertheless, the pharmacotherapy of sepsis remains an area of intense research, and ongoing clinical trials as well as continuing basic research into the pathophysiologic mechanisms of sepsis yet may yield a well-studied drug that offers survival benefit to patients with sepsis.

L8 ANSWER 16 OF 24 MEDLINE
ACCESSION NUMBER: 96116791 MEDLINE
DOCUMENT NUMBER: 96116791 PubMed ID: 8578460
TITLE: Thrombosis and inflammation as multicellular processes:

significance of cell-cell interactions.
AUTHOR: Marcus A J; Safier L B; Broekman M J; Islam N; Fliessbach J H; Hajjar K A; Kaminski W E; Jendraschak E; Silverstein R L; von Schacky C
CORPORATE SOURCE: Departement of Veterans Affairs Medical Center, New York, NY 10021, USA.
CONTRACT NUMBER: HL-18828 (NHLBI)
HL-46403 (NHLBI)
HL-47073 (NHLBI)
SOURCE: THROMBOSIS AND HAEMOSTASIS, (1995 Jul) 74 (1) 213-7. Ref: 54
Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960321
Last Updated on STN: 19960321
Entered Medline: 19960314

AB Platelet activation as a result of vascular injury provokes endothelial cells to respond in a manner which limits or reverses the occlusive consequences of platelet accumulation. If the agonistic forces are strong, platelet accumulation is irreversible. In vitro data from our laboratory have repeatedly demonstrated that platelets become unresponsive to all agonists when in proximity to endothelial cells. This unresponsiveness is due to at least three separate endothelial "thromboregulatory" systems: eicosanoids, endothelium-derived relaxing factor (EDRF/NO), and most importantly an endothelial cell ecto-nucleotidase which metabolizes released platelet adenosine diphosphate (ADP) with consequent restoration of platelets to the resting state. This nucleotidase is operative in the complete absence of EDRF/NO and eicosanoids, indicating that the latter two are dispensable thromboregulators. We have solubilized the human endothelial cell ectoADPase, as well as that from placental tissue. Candidate proteins from a purified ADPase fraction are now being studied in further detail. An understanding of the molecular biology of the ADPase gene may lead to development of therapeutic agents such as soluble forms of the enzyme as well as approaches toward up-regulation of ectoADPase activity. This could result in "early thromboregulation", i.e. prevention and/or reversal of platelet accumulation at sites of vascular damage via immediate metabolic removal of the prime platelet agonist-ADP.

L8 ANSWER 17 OF 24 MEDLINE
ACCESSION NUMBER: 96097145 MEDLINE
DOCUMENT NUMBER: 96097145 PubMed ID: 7483165
TITLE: Gene therapy to restore prostacyclin presence to injured endothelium.
AUTHOR: Willerson J T; Zoldhelyi P; Meidell R; McNatt J; Xu X M; Wu K K
CORPORATE SOURCE: University of Texas Health Science Center, Houston 77030, USA.
CONTRACT NUMBER: RO1 HL50179 (NHLBI)
T32 HL07591 (NHLBI)
SOURCE: TRANSACTIONS OF THE AMERICAN CLINICAL AND CLIMATOLOGICAL ASSOCIATION, (1994) 106 100-7; discussion 107-8. Ref: 41
Journal code: 7507559. ISSN: 0065-7778.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951221

AB These preliminary studies demonstrate the feasibility of restoration of prostacyclin synthesis in mechanically-injured porcine carotid arteries following angioplasty. Our initial data suggest the possibility of inhibiting thrombus development by adenovirus-CMV-PGHS-1 therapy in the initial 10 days following angioplasty.

L8 ANSWER 18 OF 24 MEDLINE
ACCESSION NUMBER: 96057978 MEDLINE
DOCUMENT NUMBER: 96057978 PubMed ID: 7558251
TITLE: Role of xanthine oxidase and eicosanoids in development of pancreatic ischemia-reperfusion injury.
AUTHOR: Hotter G; Closa D; Gelpi E; Prats N; Rosello-Catafau J
CORPORATE SOURCE: Department of Medical Bioanalysis, CID, CSIC, Barcelona, Spain.
SOURCE: INFLAMMATION, (1995 Aug) 19 (4) 469-78.
Journal code: 7600105. ISSN: 0360-3997.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19970203
Entered Medline: 19951122

AB The implication of different eicosanoids and oxygen free radicals in the development of pancreatic injury after an ischemia-reperfusion process has been evaluated. For this purpose we have compared the effect of allopurinol and indomethacin administration on the pancreatic levels of eicosanoids in a rat model of pancreatic ischemia-reperfusion. After 60 min of pancreatic ischemia and 2 h of reperfusion, significant increases in 6-keto-PGF1 alpha, PGE2, and LTB4 in pancreas tissue were detected. Allopurinol before the ischemic period reduced 6-keto-PGF1 alpha, PGE2, and LTB4 levels to the range of basal values, while prior indomethacin treatment significantly reduced 6-keto-PGF1 alpha and PGE2 levels, with LTB4 remaining unmodified. Increased postischemic plasma lipases were also significantly reduced by allopurinol to the range of sham-operated animals whereas indomethacin did not modify these levels. The data suggest a role for lipoxygenase metabolites in the development of pancreatic injury and the importance of the enzyme xanthine oxidase as an inductor of eicosanoid biosynthesis.

L8 ANSWER 19 OF 24 MEDLINE
ACCESSION NUMBER: 92270613 MEDLINE
DOCUMENT NUMBER: 92270613 PubMed ID: 1726125
TITLE: Interrelationships between prostanoids and skin flap survival: a review.
AUTHOR: Knight K R; Lepore D A; O'Brien B M
CORPORATE SOURCE: Microsurgery Research Centre, St Vincent's Hospital, Melbourne, Australia.
SOURCE: PROSTAGLANDINS LEUKOTRIENES AND ESSENTIAL FATTY ACIDS, (1991 Dec) 44 (4) 195-200. Ref: 78
Journal code: 8802730. ISSN: 0952-3278.

PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199206
ENTRY DATE: Entered STN: 19920710
Last Updated on STN: 19970203
Entered Medline: 19920622

L8 ANSWER 20 OF 24 MEDLINE
ACCESSION NUMBER: 91276516 MEDLINE
DOCUMENT NUMBER: 91276516 PubMed ID: 1905272
TITLE: Effects of indomethacin on prostaglandin E2 and thromboxane B2 contents of tracheal lavage fluids in premature infants.
AUTHOR: Le Guennec J C; Lauziere M; Black R; Sirois P
CORPORATE SOURCE: Department of Pediatrics, Faculty of Medicine, University of Sherbrooke, P. Q. Canada.
SOURCE: INFLAMMATION, (1991 Feb) 15 (1) 55-9.
Journal code: 7600105. ISSN: 0360-3997.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910818
Last Updated on STN: 19910818
Entered Medline: 19910801

AB A prospective longitudinal study was conducted in 14 premature infants intubated and receiving ventilatory support from birth, in order to evaluate the levels of prostaglandins E2 (PGE2) and thromboxane B2 (TxB2) in the tracheal lavage fluids (TLF) after treatment with indomethacin. Eight were treated with indomethacin, a cyclooxygenase inhibitor, for patient ductus arteriosus and the others served as controls. Infants who received indomethacin during the first postnatal week had significantly lower levels of eicosanoids in TLF during the first week. Our results suggest that levels of eicosanoids in TLF of premature infants are related to an inflammatory reaction and may serve as an index of the infant's overall clinical condition.

L8 ANSWER 21 OF 24 MEDLINE
ACCESSION NUMBER: 88199195 MEDLINE
DOCUMENT NUMBER: 88199195 PubMed ID: 3129524
TITLE: Nonsteroidal anti-inflammatory drugs correct the bactericidal defect of polymorphonuclear leukocytes in a guinea pig model of thermal injury.
AUTHOR: Bjornson A B; Knippenberg R W; Bjornson H S
CORPORATE SOURCE: Division of Immunology, James N. Gamble Institute of Medical Research,Cincinnati, Ohio 45219.
SOURCE: JOURNAL OF INFECTIOUS DISEASES, (1988 May) 157 (5) 959-67.
Journal code: 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198806
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880601

AB We conducted studies to determine the effects of parenteral therapy with indomethacin, ibuprofen, and piroxicam on key immunologic and hematologic alterations induced by thermal injury. Drugs (10-20 mg/kg) or placebo were administered intramuscularly to thermally injured guinea pigs at 3 h postburn and then daily for nine days postburn. All three drugs inhibited production of 6-keto prostaglandin F1 alpha and thromboxane B2 in wound fluid and concomitantly restored the bactericidal activity of polymorphonuclear leukocytes (PMNLs) against Pseudomonas aeruginosa to normal. Indomethacin also increased the proliferative response of splenic lymphocytes to concanavalin A; however, ibuprofen and piroxicam had no effect on this response. None of the drugs affected the extent of systemic complement consumption, thrombocytopenia, leukocytosis, or leukopenia in the injured animals. These results suggest that the PMNL bactericidal defect induced by thermal injury is preventable or reversible and that the mechanisms responsible for this defect are inhibitable by nonsteroidal anti-inflammatory drugs.

L8 ANSWER 22 OF 24 MEDLINE
ACCESSION NUMBER: 85009807 MEDLINE
DOCUMENT NUMBER: 85009807 PubMed ID: 6148428
TITLE: Should regional anesthesia and pharmacological agents such as beta blockers and opiates be utilized in modulating pain response?.
AUTHOR: Kehlet H
CONTRACT NUMBER: 5-T32-GM07612 (NIGMS)
SOURCE: JOURNAL OF TRAUMA, (1984 Sep) 24 (9 Suppl) S177-86.
Journal code: 0376373. ISSN: 0022-5282.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198411
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19970203
Entered Medline: 19841101

L8 ANSWER 23 OF 24 MEDLINE
ACCESSION NUMBER: 80203361 MEDLINE
DOCUMENT NUMBER: 80203361 PubMed ID: 6769796
TITLE: Cerebral oedema and blood-brain and blood-CSF barriers in experimental brain trauma: effect of indomethacin-A prostaglandin synthetase inhibitor.
AUTHOR: Mohanty S; Ray A K; Dey P K
SOURCE: INDIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, (1980 Apr-Jun) 24 (2) 91-6.
Journal code: 0374707. ISSN: 0019-5499.
PUB. COUNTRY: India
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198008
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19900315
Entered Medline: 19800828
AB Cerebral oedema often occurs following trauma to the brain. Recently several biogenic amines have been suggested for their possible mediation in the pathophysiology of traumatic brain oedema. The present investigation indirectly indicates that prostaglandins of E series are also involved in the etiology of cerebral oedema, since administration of a potent PG synthetase inhibitor, indomethacin significantly diminished

dematous swelling of traumatised rat brain.

L8 ANSWER 24 OF 24 MEDLINE
ACCESSION NUMBER: 80076656 MEDLINE
DOCUMENT NUMBER: 80076656 PubMed ID: 159985
TITLE: On the enzymatic response to injury and its mediators.
AUTHOR: Raekallio J; Nieminen L
SOURCE: MEDICAL BIOLOGY, (1979 Aug) 57 (4) 211-9.
Journal code: 0417300. ISSN: 0302-2137.
PUB. COUNTRY: Finland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198002
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19970203
Entered Medline: 19800228

AB The enzymatic response to injury appears as an increase in enzymatic activity in the periphery of burns and other injuries. The following processes constitute the enzymatic response: 1) release, 2) activation and 3) synthesis of enzymes. Processes 2) and 3) are dependent upon the fibroblast, which is an activated fibrocyte. Among the fibrocyte activators, and thus among the mediators of the enzymatic response, are histamine, serotonin, kinins, prostaglandins etc. The effects of non-steroidal anti-inflammatory drugs on the enzymatic response to burn injury were studied. Indomethacin, mefenamic acid or aspirin, suspended in carboxymethylcellulose, were given to rats by stomach tube. Controls received carboxymethylcellulose only. Circular burns were inflicted on anaesthetized animals which were killed 30 min, 2 h or 4 h after burning. The burns were studied histologically and enzyme histochemically by using the methods for prostaglandin synthetase, esterases, and adenosine triphosphatase. Aspirin had no effect on the enzymatic response. Mefenamic acid and indomethacin caused a less severe enzymatic response in the 4-h groups as compared to control rats.